

University of Groningen

Remodeling of the interstitial extracellular matrix in white matter multiple sclerosis lesions

de Jong, Jody M.; Wang, Peng; Oomkens, Michelle; Baron, Wia

Published in:
Journal of Neuroscience Research

DOI:
[10.1002/jnr.24582](https://doi.org/10.1002/jnr.24582)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2020

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

de Jong, J. M., Wang, P., Oomkens, M., & Baron, W. (2020). Remodeling of the interstitial extracellular matrix in white matter multiple sclerosis lesions: Implications for remyelination (failure). *Journal of Neuroscience Research*, 98(7), 1370-1397. <https://doi.org/10.1002/jnr.24582>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

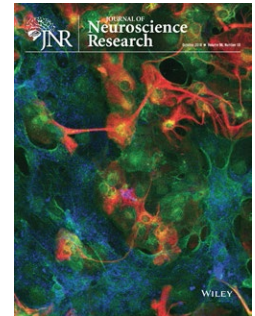
Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

REVIEW

Remodeling of the interstitial extracellular matrix in white matter multiple sclerosis lesions: Implications for remyelination (failure)

Jody M. de Jong | Peng Wang | Michelle Oomkens | Wia Baron 

Section Molecular Neurobiology, Biomedical Sciences of Cells & Systems, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands

Correspondence

Wia Baron, Section Molecular Neurobiology, Biomedical Sciences of Cells & Systems, University Medical Center Groningen, University of Groningen, A. Deusinglaan 1, 9713 AV Groningen, the Netherlands.
Email: w.baron@umcg.nl

Present address

Peng Wang, Ningxia Key Laboratory of Cerebrocranial Diseases, School of Basic Medical Science, Ningxia Medical University, Yinchuan, China

Funding information

Work in the Baron Laboratory is supported by grants from the Dutch MS Research Foundation (Stichting MS Research, 18-733c MS, J.M.d.J.). P.W. is a recipient of a China Scholarship Council (CSC) fellowship (201306300077)

Abstract

The extracellular matrix (ECM) provides protection, rigidity, and structure toward cells. It consists, among others, of a wide variety of glycoproteins and proteoglycans, which act together to produce a complex and dynamic environment, most relevant in transmembrane events. In the brain, the ECM occupies a notable proportion of its volume and maintains the homeostasis of central nervous system (CNS). In addition, remodeling of the ECM, that is transient changes in ECM proteins regulated by matrix metalloproteinases (MMPs), is an important process that modulates cell behavior upon injury, thereby facilitating recovery. Failure of ECM remodeling plays an important role in the pathogenesis of multiple sclerosis (MS), a neurodegenerative demyelinating disease of the CNS with an inflammatory response against protective myelin sheaths that surround axons. Remyelination of denuded axons improves the neuropathological conditions of MS, but this regeneration process fails over time, leading to chronic disease progression. In this review, we uncover abnormal ECM remodeling in MS lesions by discussing ECM remodeling in experimental demyelination models, that is when remyelination is successful, and compare alterations in ECM components to the ECM composition and MMP expression in the parenchyma of demyelinated MS lesions, that is when remyelination fails. Inter- and intralesional differences in ECM remodeling in the distinct white matter MS lesions are discussed in terms of consequences for oligodendrocyte behavior and remyelination (failure). Hence, the review will aid to understand how abnormal ECM remodeling contributes to remyelination failure in MS lesions and assists in developing therapeutic strategies to promote remyelination.

Abbreviations: BBB, blood–brain barrier; CNS, central nervous system; CSF, cerebrospinal fluid; CSPGs, chondroitin sulfate proteoglycans; EAE, experimental autoimmune encephalomyelitis; ECM, extracellular matrix; GAG, glycosaminoglycans; HMW hyaluronan, high-molecular weight hyaluronan; LMW hyaluronan, low-molecular weight hyaluronan; MBP, myelin basic protein; MMP, matrix metalloproteinase; MS, multiple sclerosis; MT-MMP, membrane-type matrix metalloproteinase; NAWM, normal appearing white matter; OPC, oligodendrocyte progenitor cell; TIMP, tissue inhibitor of metalloproteinase; TME, Theiler's murine encephalomyelitis.

Jody M. de Jong, Peng Wang, and Michelle Oomkens should be considered joint first author.

Edited by Bradley Kerr and Eric Prager. Reviewed by Voon Wee Yong and Luke Healy.

The peer review history for this article is available at <https://publons.com/publon/10.1002/jnr.24582>.

This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

© 2020 The Authors. Journal of Neuroscience Research published by Wiley Periodicals, Inc.

KEYWORDS

extracellular matrix, matrix metalloproteinase, multiple sclerosis, oligodendrocyte, remyelination

1 | INTRODUCTION

The extracellular space of all organs and tissues is composed of a network of molecules, essential for physical support of cellular components and many cellular processes. This highly organized three-dimensional molecular network is called the extracellular matrix (ECM). The ECM composition is specific for each organ or tissue, but the majority of components is comprised of proteoglycans, hyaluronan, and fibrous (glyco)proteins, such as collagens, elastin, fibronectin and laminin, and non-structural regulators, that is matricellular proteins such as tenascins, CCNs, SPARCs, fibulins, osteopontin, and thrombospondins (Theocharis, Skandalis, Gialeli, & Karamanos, 2016). These components act together to produce a complex and dynamic environment, involved in cell surface and transmembrane events. Next to being a physical scaffold in which cells are embedded, ECM binds to adhesion receptors on cells, such as integrins, thereby regulating numerous cellular processes, including cell migration, differentiation, proliferation, and survival (Rozario & DeSimone, 2010). Furthermore, the ECM functions as a reservoir for growth factors and other signaling molecules, thereby influencing cell behavior indirectly. It may also act as a diffusion and migration barrier. Essentially all cell types synthesize and secrete ECM molecules. Variations in the composition and structure of ECM components affect both the overall structure and bioactive properties of the ECM, thereby affecting signal transmission and thus the cellular response. The ECM is crucial for homeostasis, and is actively involved in repairing injury, whereas pathological conditions emerge from abnormalities in the ECM components.

In the central nervous system (CNS), the extracellular space takes up 17%–20% of the adult brain volume (Cragg, 1979; Nicholson & Sykova, 1998). Remarkably, while the ECM undergoes dynamic and continuous remodeling, mediated by matrix-degrading enzymes at normal and pathological conditions, ECM remodeling in the healthy adult CNS is very limited (Dityatev & Fellin, 2008; Rauch, 2007). As in all tissues, the ECM in the CNS can be classified in two major types that vary in structure, composition and regional appearance: the pericellular matrices that are in close contact with cells and the interstitial matrices that surround cells. Examples of pericellular matrices in the CNS include (a) the vascular and astroglial basement membranes that are present at the interface between endothelial cells and astrocytes, which play an important role in blood–brain barrier (BBB) maintenance (Lau, Cua, Keough, Haylock-Jacobs, & Yong, 2013; Schreibelt et al., 2007; van Horssen, Dijkstra, & de Vries, 2007) and (b) neuronal-associated perineuronal nets that emerge during synaptogenesis, which preserve neuronal health by maintaining synaptic plasticity (Frischknecht & Seidenbecher, 2008;

Significance

Demyelination and failure to remyelinate contribute to the neurological deficits that characterize the chronic progressive disease multiple sclerosis. Components of the extracellular matrix are involved in guiding each stage of the remyelination process, including oligodendrocyte progenitor cell migration, proliferation, and maturation. This review highlights the importance of extracellular matrix remodeling in successful remyelination and links dysregulated matrix metalloproteinase expression in white matter multiple sclerosis lesions to abnormal inter- and intralesional expression patterns of ECM components and remyelination failure. Hence, this review will assist in developing therapeutic strategies to overcome remyelination failure and halt disease progression.

Kwok, Dick, Wang, & Fawcett, 2011; Oohashi, Edamatsu, Bekku, & Carulli, 2015). The dispersed ECM in the CNS parenchyma is a representative example of an interstitial matrix. The interstitial ECM in healthy adult CNS contains relatively low levels of fibrous matrix proteins, like collagen, fibronectin, and laminin, which are mainly restricted to basement membranes (Ruoslahti, 1996; van Horssen et al., 2007). Instead, the adult interstitial ECM contains high levels of glycosaminoglycans (GAGs), either covalently attached to proteins, forming mainly chondroitin sulfate proteoglycans (CSPGs), particular lecticans, such as aggrecan, versican, and neurocan, or as unbound entities in the form of hyaluronan (Kwok et al., 2011; Rauch, 2007; Ruoslahti, 1996). Hyaluronan is the major component of healthy CNS, and is connected to CSPGs via linker proteins (Bignami, Hosley, & Dahl, 1993). Additional components of the adult ECM include the matricellular proteins of which tenascin-R and thrombospondin are most prominent in the CNS (Jones & Bouvier, 2014; Kwok et al., 2011). Notably, the perineuronal nets are enriched in hyaluronan, tenascin-R, and CSPGs. All cell types of the CNS, that is astrocytes, microglia, oligodendrocytes, and neurons, as well as endothelial cells, contribute to the pool of proteins that eventually constitute the ECM (Lau et al., 2012).

The ECM of the CNS plays an important role in many regulatory processes during development and in the homeostasis of healthy adult CNS. In response to injury, the composition of the ECM changes, resulting in a transient ECM environment that may be either stimulatory or inhibitory to repair. Different neuropathological conditions are associated with a dysregulation of alterations in the expression pattern of ECM molecules, thereby impeding the

process of repair, including regeneration. For example, a role of the dynamics and the distinct involvement of ECM components is becoming increasingly apparent in the demyelinating disease multiple sclerosis (MS), showing an association between ECM alterations and white matter MS lesion formation (Satoh, Tabunoki, & Yamamura, 2009) and progression of the neuropathological state (Bonneh-Barkay & Wiley, 2009). ECM remodeling is tightly regulated by an interplay between several proteins and enzymes of which the family of matrix metalloproteinase (MMP) is a prominent proteolytic system in the spatiotemporal regulation of the ECM (Lu, Takai, Weaver, & Werb, 2011; Page-McCaw, Ewald, & Werb, 2007). Functional dysregulation of these enzymes contributes to the pathogenesis and progression of several inflammatory demyelinating diseases, including MS (Kieseier, Seifert, Giovannoni, & Hartung, 1999). Here, we aim to unravel abnormal ECM remodeling in MS lesions and link this to remyelination failure, as to assist in developing therapeutic strategies to promote remyelination in MS. To this end, we uncover abnormal ECM remodeling in MS lesions by describing and comparing the transient-altered expression patterns of individual ECM molecules and MMPs upon successful CNS remyelination in rodent models of toxin-induced demyelination, and upon remyelination failure in MS lesions. In addition, we discuss how the (transiently) expressed ECM proteins regulate the behavior of cells that produce myelin, that is oligodendrocytes, and how their (persistent) expression may contribute to remyelination (failure). Also, the interactions between ECM molecules and MMPs and potential mechanisms leading to incorrect ECM remodeling in MS are reviewed. Before discussing this in more detail, we first present a brief overview of the pathology of MS.

2 | MULTIPLE SCLEROSIS

2.1 | Pathological hallmarks

MS is a neurodegenerative inflammatory disease of the CNS. It is one of the most common demyelinating CNS diseases with an incidence of approximately 0.1% worldwide, while the prevalence varies based on geographical and ethnical differences (Compston & Coles, 2008; Rosati, 2001). Variable patterns of the clinical course of MS are observed. The most common form is relapsing-remitting MS, which is diagnosed in about 80% of the MS patients (Lublin & Reingold, 1996). Relapsing-remitting MS is characterized by relapses followed by full or partial recovery at the onset of the disease, but incomplete recovery arises over time and the majority of patients develop secondary progressive MS with minor remissions (Compston & Coles, 2008). Primary progressive MS is diagnosed in 10%–20% of the patients (Lublin & Reingold, 1996), has an onset at a later age, and is characterized by gradual accumulation of neurological deficits, starting already at the onset of the disease (Compston & Coles, 2008).

The disease is characterized by chronic and progressive loss of myelin sheaths surrounding the axons in the brain and spinal cord.

The primary causative mechanism(s) resulting in demyelination and progression of MS is (are) still unclear. However, genetic predisposition, that is mainly genes implied in (cell-mediated) immunity, and several environmental factors, such as vitamin D deficiency and viral infections, appear to play an important role in the development of MS (Compston & Coles, 2008; Correale & Gaitan, 2015; Olsson, Barcellos, & Alfredsson, 2017; Roch et al., 2017). These factors contribute to the inflammatory process occurring in MS, which is associated with disruption of the BBB. Whether this inflammation is a primary or secondary event in the pathogenesis of MS is unknown (Compston & Coles, 2008; Stys, Zamponi, van Minnen, & Geurts, 2012). An autoimmune response is initiated in the periphery through (as yet unknown) processes. Molecular mimicry might underlie such an event, resulting in activation of autoreactive T cells against self-antigens, which migrate to the CNS. Subsequently, this might initiate an immune response, thus causing damage and degeneration. In contrast, cytodegenerative processes in the CNS through (as yet equally unknown) factors may activate autoreactive T cells by presentation of self-antigens and subsequently induce a secondary immune response. In MS, these autoreactive T cells are directed to self-antigens that include specific proteins, present on the surface of mature oligodendrocytes and/or in myelin (Mallucci, Peruzzotti-Jametti, Bernstock, & Pluchino, 2015). This results in (additional) demyelination due to the destruction of myelin and/or mature oligodendrocytes.

The formation of white matter MS lesions is a dynamic process resulting in interlesional heterogeneity. More specifically, distinct lesions are histopathologically classified in inflammatory and demyelinating activity (Kuhlmann et al., 2017; van der Valk & De Groot, 2000). While different classification systems have been described, mainly three distinct lesions can be distinguished: active, mixed active/inactive, and inactive lesions (Figure 1, (Kuhlmann et al., 2017)). Active lesions are the early demyelinating phenotype and are most frequently found in acute MS patients with a very short disease duration (Frischer et al., 2015), while their proportion (approx. 25%) is similar upon longer disease duration and severity (Frischer et al., 2015; Luchetti et al., 2018). Active lesions are defined by indistinct margins, harbor inflammatory activity, and contain a hypercellular lesion center with hypertrophic astrocytes, (myelin-laden) microglia/macrophages, and lymphocytes. Mixed active/inactive lesions (also called “chronic active lesions” or “smoldering lesions”) show intralesional heterogeneity having a sharp border and consist of a hypocellular demyelinated lesion center with fibrous astrocytes. The lesion center is surrounded by a broad hypercellular inflammatory rim that contains microglia/macrophages and reactive astrocytes. The mixed active/inactive lesions are more frequently observed in progressive MS patients than in relapsing-remitting MS patients (Frischer et al., 2015; Luchetti et al., 2018). The final lesion classification is a (chronic) inactive MS lesion. These lesions have a hypocellular demyelinated center, containing mainly reactive astrocytes and show hardly signs of infiltration of microglia/macrophages or lymphocytes. Inactive lesions are also predominating in progressive MS (Frischer et al., 2015).

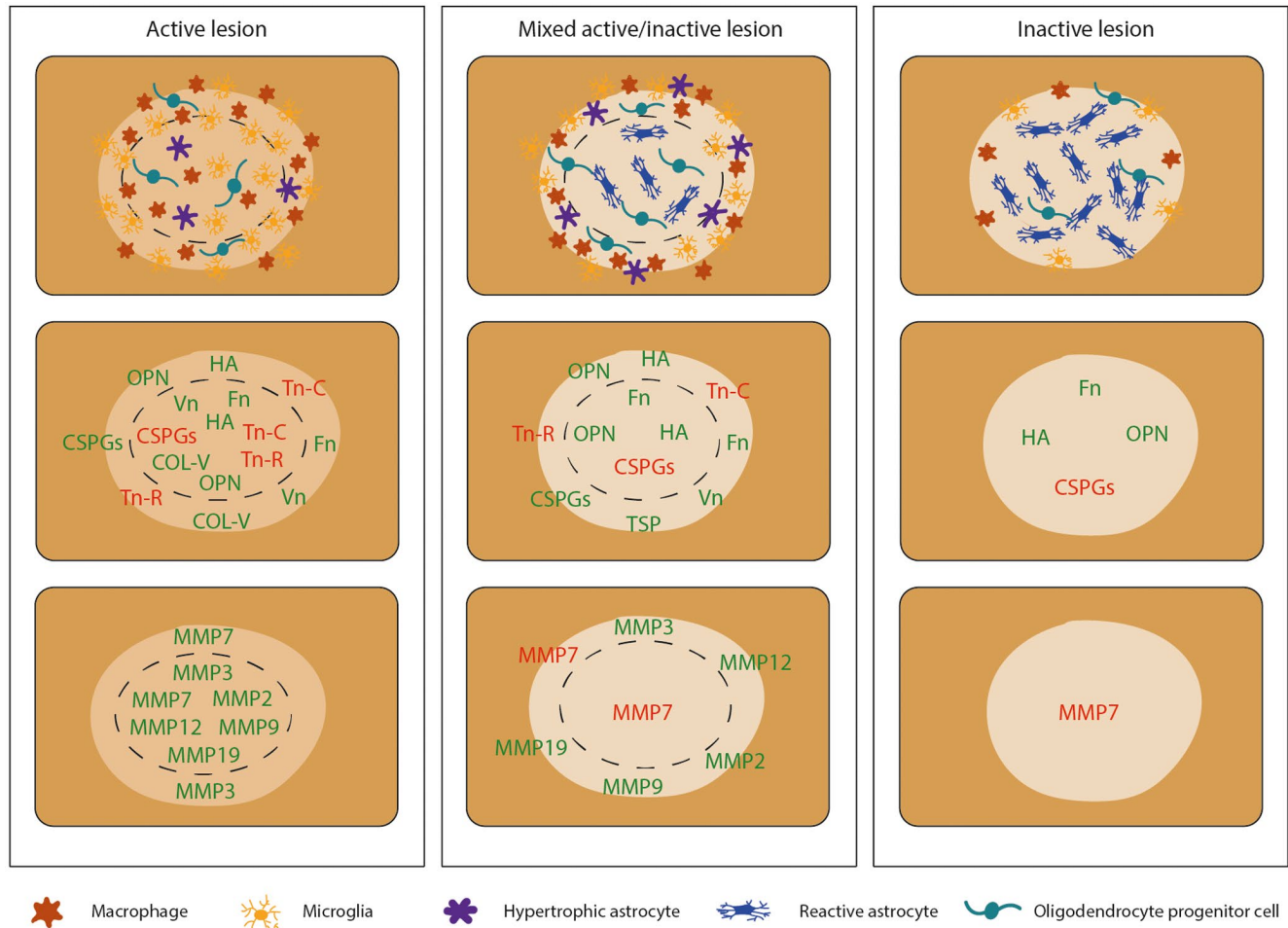


FIGURE 1 Schematic overview of the inter- and intralesional heterogeneity of cells, extracellular matrix (ECM) proteins, and matrix metalloproteinases (MMPs) in active, mixed active/inactive and inactive white matter multiple sclerosis lesions. Lesions are indicated as pale (demyelinated) areas. ECM proteins and MMPs depicted in green have an increased expression and ECM proteins and MMPs depicted in red have a decreased expression compared to control white matter at the indicated location of the lesion, that is lesion center or rim. COL-V, collagen V; CSPGs, chondroitin sulfate proteoglycans; Fn, fibronectin; HA, hyaluronan; OPN, osteopontin; Tn-C, tenascin-C; Tn-R, tenascin-R; Vn, vitronectin. Thrombospondin-1 expression is increased in mixed active/inactive and inactive lesions, while data on localization are not available yet

2.2 | Failure of remyelination

Myelin is an insulating layer around axons that provides axonal protection and electrical isolation, and mediates saltatory conduction of action potentials. The loss of activity due to demyelination is partially compensated by a redistribution of sodium channels along the demyelinated parts of the axon, which allows for non-saltatory conduction with reduced velocity (Felts, Baker, & Smith, 1997). However, this compensatory effect is only temporal and in conjunction with the loss of axonal protection, persistent demyelination leads to axonal damage and degeneration (Compston & Coles, 2008; Funfschilling et al., 2012; Lee et al., 2012). The rate of impulse transduction is reduced or the impulses cease, which results in clinical signs and symptoms of MS that reflect the affected area of the CNS (Compston & Coles, 2008). In addition, accumulation of axonal degeneration is the main process that contributes to progression of neurological dysfunction and disease

severity (Compston & Coles, 2008; Papadopoulos, Pham-Dinh, & Reynolds, 2006). Progressive axonal loss is key to the continuous and irreversible neurological decline in progressive MS (Trapp & Nave, 2008). Next to primary axon damage, a major cause of axonal loss in chronic stages of MS is secondary neurodegeneration as a consequence of remyelination failure (Irvine & Blakemore, 2008). Indeed, in addition to ensure saltatory axonal conduction, myelinating oligodendrocytes secrete metabolic and trophic factors that maintain the integrity and survival of axons (Funfschilling et al., 2012; Lee et al., 2012). Therefore, prevention of axonal degeneration might be beneficial to resolve the functional deficits and progression of MS.

A regenerative process to restore myelin is required to ensure the survival of demyelinated axons. This process is called remyelination, which re-establishes saltatory conduction, protects axons from degeneration and improves clinical features of MS (Franklin & French-Constant, 2008; Franklin, Zhao, & Sim, 2002; Irvine &

Blakemore, 2008; Jeffery & Blakemore, 1997; Smith, Blakemore, & McDonald, 1979). The myelin sheaths generated in the process of remyelination are shorter and thinner, compared to myelin sheaths produced during developmental myelination, but these newly-formed sheaths suffice for axonal protection and improved functioning (Kornek et al., 2000). Experimental demyelination in rodent models show that successful remyelination is not executed by pre-existing mature oligodendrocytes but achieved by newly-formed oligodendrocytes generated from local oligodendrocyte progenitor cells (OPCs; Zawadzka et al., 2010), while OPCs present in the adult subventricular zone contribute predominantly to remyelination of lesions in their proximity (Menn et al., 2006). In response to toxin-induced demyelination in these models, astrocytes and microglia are activated (reviewed by Franklin & ffrench-Constant, 2008; Franklin et al., 2002). These changes lead to the (transcriptional) activation of OPCs, resulting in morphological changes and enhanced gene expression of factors involved in oligodendrocyte differentiation and maturation (Arnett et al., 2004; Ferent, Zimmer, Durbec, Ruat, & Traiffort, 2013; Moyon et al., 2015; Reynolds et al., 2002; Watanabe, Hadzic, & Nishiyama, 2004). In addition to OPC activation, microglia and astrocytes recruit and mediate the migration of OPCs to the demyelinated areas, where they further proliferate (Franklin & ffrench-Constant, 2008; Franklin et al., 2002; Levine & Reynolds, 1999). The final essential step is the generation of new myelin sheaths and involves the differentiation of OPCs into mature oligodendrocytes. The process includes contact between the oligodendrocyte and the axon, upregulation of myelin-specific genes and generation and compaction of the myelin membranes (Franklin & ffrench-Constant, 2008; Franklin et al., 2002). While in experimental rodent models remyelination is executed by OPCs, carbon 14-based birth dating and single nuclei RNA sequencing of MS brain tissue reveal that remyelination in MS is most likely not executed by OPCs, but by pre-existing mature oligodendrocytes (Jakel et al., 2019; Schirmer et al., 2019; Yeung et al., 2019). Whether this is an inherent capacity of remyelination in humans, or an adaptation as of the inability of OPCs to differentiate to mature myelinating oligodendrocytes in MS lesions remains to be determined. However, in both cases, that is remyelination by newly-formed or pre-existing OLGs, new myelin membranes are formed.

A plethora of molecules play an important role in the different phases of remyelination, as well as several mediators of the inflammatory response, featuring in MS (Franklin & ffrench-Constant, 2008; Franklin et al., 2002; Gaesser & Fyffe-Maricich, 2016; Hanafy & Sloane, 2011; Miron, 2017). Although remyelination is a natural response to demyelination in most cases, this regenerative process often fails in chronic and progressive MS (Compston & Coles, 2008; Franklin & ffrench-Constant, 2008; Goldschmidt, Antel, Konig, Bruck, & Kuhlmann, 2009; Kuhlmann et al., 2008; Lucchinetti et al., 1999; Luchetti et al., 2018). In a subset of lesions, insufficient migration and/or proliferation of OPCs likely accounts for remyelination failure. However, remyelination mainly fails due to defective OPC differentiation (Franklin & ffrench-Constant, 2008; Franklin et al., 2002; Kuhlmann et al., 2008). In fact, in approx. 70% of both active and

chronic MS lesions, OPCs are abundantly present (Chang, Tourtellotte, Rudick, & Trapp, 2002; Goldschmidt et al., 2009; Kuhlmann et al., 2008; Lucchinetti et al., 1999; Strijbis, Kooi, van der Valk, & Geurts, 2017; Wolswijk, 1998). Of interest in this respect is that single nuclei RNA sequencing of MS brain tissue shows that more dysregulated genes are found in mature oligodendrocytes rather than in OPCs compared to tissue of healthy subjects (Schirmer et al., 2019). This may indicate that OPCs are indeed transcriptionally relatively quiescent in MS, likely as a reflection of the inhibitory environment in MS lesions for OPC differentiation. Remyelination not always fails in MS, given the presence of partly or completely remyelinated shadow plaques. Remyelinated shadow plaques are present at all stages of MS (Frischer et al., 2015; Goldschmidt et al., 2009; Kuhlmann et al., 2017; Luchetti et al., 2018) and is thus likely executed by pre-existing oligodendrocytes (Jakel et al., 2019; Yeung et al., 2019), but the frequency of remyelinated white matter shadow plaques is lower in the progressive forms compared to relapsing-remitting MS (Luchetti et al., 2018). This is likely a reflection of remyelination failure in mixed active/inactive lesions that are dominating at later stages. Notably, although extensive remyelination is occasionally observed at late-stage progressive MS (Patani, Balaratnam, Vora, & Reynolds, 2007; Patrikios et al., 2006), it is most prominently noted in acute lesions, that is immediately upon demyelination (Prineas et al., 1989; Raine & Wu, 1993).

Remyelination failure is thus thought to be a consequence of perturbations in the different phases of remyelination, that is activation, recruitment, and differentiation of OPCs, in which aging also plays an important role (Franklin & ffrench-Constant, 2008; Goldschmidt et al., 2009; Sim, Zhao, Penderis, & Franklin, 2002). The signaling and cellular environment, established by the state of the disease and lesion regulating these phases, is a crucial factor. Remyelination failure in MS is likely due to the presence of inhibitory signals or the lack of stimulatory signals in the damaged area. Indeed, various factors in the signaling environment of MS lesions are dysregulated, and together with ensuing cellular changes contribute to the failure of remyelination (Franklin & ffrench-Constant, 2008; Franklin et al., 2002; Hanafy & Sloane, 2011; Miron, 2017; Williams, Piaton, & Lubetzki, 2007). In this regard, a role of the dynamics and distinct interstitial ECM components in remyelination failure in MS lesions is becoming increasingly apparent (Lau et al., 2013; Satoh et al., 2009). In contrast, ECM remodeling benefits remyelination upon toxin-induced demyelination in rodent models, pointing to abnormal ECM remodeling in MS lesions, which is reviewed next.

3 | THE INTERSTITIAL ECM UPON DEMYELINATING INJURY

Dynamic remodeling of the ECM, that is transient expression and/or degradation, is an effective mechanism to regulate glial cell behavior, including OPCs upon injury (reviewed in (Pu, Stephenson, & Yong, 2018)). Analysis of mRNA expression of ECM proteins and the MS lesion proteome reveals that mixed active/inactive and inactive MS lesions have a unique ECM composition, both when compared

among each other and to control white matter and active MS lesions (Hendrickx et al., 2017; Mohan et al., 2010; Satoh et al., 2009). This hints to interlesional heterogeneity of ECM proteins in MS lesions and that dysregulated ECM remodeling may play an important role in the pathogenesis of MS, including remyelination failure. To unravel abnormal ECM composition in the distinct MS lesions, experimental toxin-induced demyelination rodent models that show robust remyelination in the absence of the complex inflammatory background in MS are most instructive to obtain insight into the natural cellular and molecular responses during demyelination of the CNS and subsequent successful recovery. These toxin-induced demyelination models include the dietary cuprizone model (mice), which shows global demyelination most prominently in the corpus callosum (Praet, Guglielmetti, Berneman, Van der Linden, & Ponsaerts, 2014; Skripuletz, Gudi, Hackstette, & Stangel, 2011; Torkildsen, Brunborg, Myhr, & Bo, 2008), and the focal lysolecithin (mice and rat) and ethidium bromide (mice) models, where demyelination is induced by local injection of the toxin in the area of interest (Blakemore, 1976; Jeffery & Blakemore, 1995; Zhao, Li, & Franklin, 2006). Notably, in the lysolecithin model the BBB is disrupted (Muramatsu et al., 2015), while the endothelial cells remain seemingly intact in the cuprizone and ethidium bromide model (Bjelobaba, Begovic-Kupresanin, Pekovic, & Lavrnja, 2018; Kondo, Nakano, & Suzuki, 1987; McMahon, Suzuki, & Matsushima, 2002). In the following, we outline for each ECM protein transient changes in its expression in the interstitial matrix, that is parenchymal ECM, upon

white matter demyelination and during remyelination in experimental rodent models, and indicate its presence in the distinct white matter MS lesions (summarized in Table 1 and Figure 1). In addition, we discuss direct effect(s) of each ECM protein on OPC behavior (summarized in Figure 2) and discuss how the protein may contribute to remyelination (failure). We only briefly touch upon changes in ECM composition of basement membranes, as remyelination-predetermined OPCs in general do not face the ECM in basement membranes. For irregularities and alterations of ECM in basement membranes, we refer to two excellent reviews by van Horssen et al. (2007) and Lau et al. (2013).

3.1 | Structural ECM proteins

CSPGs are the main proteoglycans of the CNS and consist of core proteins with covalently linked sulfated chondroitin GAG side chains. The individual secreted CSPGs, that is neurocan, aggrecan, versican, and phosphacan, differ in the composition of their core protein and/or the number and type of attached GAG chains. CSPGs can be produced by astrocytes, microglia/macrophages, neurons, and oligodendrocytes (Asher et al., 2002; Hibbits, Yoshino, Le, & Armstrong, 2012; Keough et al., 2016; Lau et al., 2012). CSPG expression, including versican and phosphacan, but not aggrecan, transiently increases upon lysolecithin- (Keough et al., 2016; Lau et al., 2012) and/or cuprizone-induced demyelination

TABLE 1 Expression of interstitial ECM proteins upon toxin-induced demyelination and in distinct white matter MS lesions

ECM proteins	Experimental rodent models		Multiple sclerosis				
			Active		Mixed active/inactive		
	Demyelination	Remyelination	Edge	Center	Edge	Center	Inactive
CSPGs	↑	=	↑	↓	↑	↓	↓
-Neurocan	n.d.	n.d.	↑	↓	↑	↓	↓
-Aggrecan	=	n.d.	↑	↓	↑	↓	↓
-Versican	↑	=	↑	↓	↑	↓	↓
-Phosphacan	↑	=	=	=	=	=	=
Hyaluronan	=	=	↑		↑		↑
Collagen (V)	=	=	↑		=		=
Fibronectin	↑	=	↑		↑(aggregates ^a)		↑(aggregates ^a)
Vitronectin	↑	=	↑		↑	=	=
Laminin	=	↑	=		=		=
Tenascins							
Tenascin-C	↑	=	↓		↓	=	=
Tenascin-R	↑	=	↓		↓	=	=
Thrombospondin	↑	n.d.	=		↑ ^b		= ^b
Osteopontin	↑	=	↑		↑		↑

Note: Increased (↑), decreased (↓), and similar (=) expression of interstitial ECM proteins upon toxin-induced demyelination and in distinct white matter MS lesions compared to control.

Abbreviation: n.d., not determined.

^aBased on biochemical analysis (Stoffels et al., 2013).

^bBased on MS lesion proteome (Satoh et al., 2009) and Western blot analysis (Sikkema et al., 2018), data on localization are not available yet.

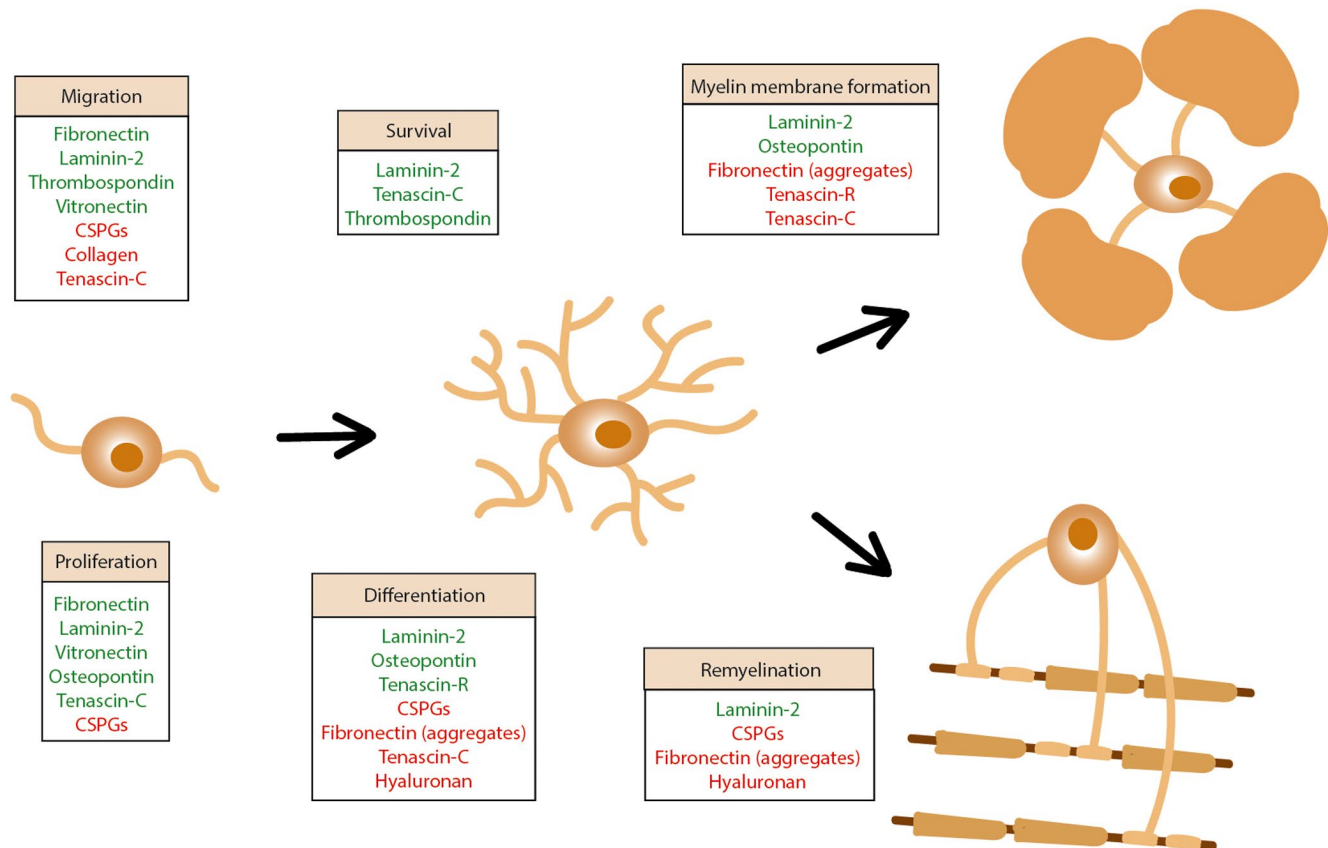


FIGURE 2 Effect of extracellular matrix (ECM) proteins on oligodendrocyte progenitor cell (OPC) behavior relevant to remyelination. Successful remyelination upon central nervous system (CNS) demyelination in experimental rodent models involves the activation of adjacent OPCs, followed by recruitment (migration and proliferation) to and maturation (process arborization, differentiation, and myelin membrane formation) in the demyelinated area. The effect of structural ECM proteins, fibrous ECM glycoproteins, and matricellular proteins that are present in the interstitial ECM upon toxin-induced CNS white matter demyelination and/or distinct white matter MS lesions are shown. ECM proteins depicted in green increase and ECM proteins depicted in red decrease the indicated OPC behavior

(Hibbitts et al., 2012). In lyssolecithin-induced lesions, CSPGs are present in microglia/macrophages at the lesion center, while astrocytes harbor CSPGs at the lesion edges (Lau et al., 2012). Depositions of CSPGs, including aggrecan, neurocan and versican, are present in astrocyte-enriched edges of active and inactive MS lesions, while their expression is downregulated in the center of active, mixed active/inactive and in inactive lesions (Dahl, Perides, & Bignami, 1989; Hendrickx et al., 2017; Sobel & Ahmed, 2001). Gene expression profiling of rim and center of mixed active/inactive and inactive MS lesions revealed that neurocan mRNA is enriched at the rim of mixed active/inactive lesions (Hendrickx et al., 2017). Deposited CSPG components in active MS lesions are suggested to be phagocytosed by foamy macrophages together with myelin debris (Sobel & Ahmed, 2001), although expression of CSPGs by macrophages cannot be excluded (Lau et al., 2012). Strikingly, phosphacan expression, which is a CNS-specific CSPG, is more or less preserved in active lesions, and, in general, less reduced in inactive MS lesions compared to the other CSPGs (Sobel & Ahmed, 2001). Also, *in situ* hybridization studies show the presence of phosphacan mRNA in remyelinating oligodendrocytes in

MS lesions (Harroch et al., 2002), and suggested to be involved in oligodendrocyte lineage progression (Karus et al., 2016). Of interest, granular aggregates of versican and aggrecan, and to a lesser extent of neurocan, but not phosphacan are evident in normal appearing white matter (NAWM; Sobel & Ahmed, 2001). This indicates that ECM alterations in MS are not limited to the lesions themselves. *In vitro* studies revealed that CSPG coatings, including aggrecan, neurocan, and phosphacan, inhibit OPC adhesion, process outgrowth and differentiation, likely by activating Rho-kinase-dependent signaling pathways via PTP σ (Keough et al., 2016; Lau et al., 2012; Lucchinetti et al., 1999; Pendleton et al., 2013; Siebert & Osterhout, 2011), as well as OPC migration *in vivo* (Siebert, Stelzner, & Osterhout, 2011). Exposure to soluble CSPGs impairs process outgrowth, but not differentiation (Lau et al., 2012; Pendleton et al., 2013). Moreover, *soluble* phosphacan is a ligand for oligodendroglial contactin and this complex inhibits OPC proliferation, and promotes OPC differentiation (Lamprianou, Chatzopoulou, Thomas, Bouyain, & Harroch, 2011). Thus, demyelination in experimental models leads to the upregulation of CSPGs, which may have beneficial functions at early stages

of recovery, that is to prevent premature OPC differentiation. Moreover, CSPGs are cleared to enable remyelination. Deposition of CSPGs in MS lesion edges may lead to the formation of a barrier for OPC migration into the lesions, and loss of CSPGs in the center may preclude their beneficial actions after recovery (Keough et al., 2016; Lau et al., 2012; Pu et al., 2018; Sobel & Ahmed, 2001).

Hyaluronan is a specialized non-sulfated GAG that functions as free, that is independent GAG molecule without protein core, or engages in non-covalent interactions with proteoglycans, including CSPGs (Sherman et al., 2002). Hyaluronan is expressed in different sizes, performing its functions in cell growth and motility and interactions between different ECM molecules to stabilize the ECM (Bignami et al., 1993). Upon lysolecithin-induced demyelination, only a minimal accumulation of hyaluronan is noticed (Back et al., 2005), suggesting that there is no major upregulation of hyaluronan after demyelinating injury in this experimental rodent model. However, deposition of hyaluronan is associated with MS development (Nagy et al., 2019). In contrast to other glycosaminoglycans (Sobel & Ahmed, 2001), hyaluronan accumulates in the core of inflammatory demyelinating active MS lesions (Back et al., 2005). In early lesions, infiltrating T cells and microglia probably produce hyaluronan and in chronic lesions, astrocytes are the likely source (Back et al., 2005). Also, OPCs, and to a lesser extent mature oligodendrocytes, synthesize hyaluronan (Preston et al., 2013). Most interestingly, T cells and microglia produce low-molecular weight hyaluronan ranging from 200 to 400 kDa (LMW hyaluronan), whereas astrocytes produce hyaluronan with high-molecular weight, ranging from 900 to 1,000 kDa (HMW hyaluronan; Back et al., 2005). Both HMW and LMW hyaluronan are present in MS lesions (Back et al., 2005; Preston et al., 2013). HMW hyaluronan is detrimental for remyelination when injected in lysolecithin-induced demyelinated lesions (Back et al., 2005). Treatment with *soluble* HMW hyaluronan or LMW hyaluronan inhibits OPC maturation through LMW hyaluronan-mediated activation of TLR2 (Back et al., 2005; Sloane et al., 2010). In fact, OPC maturation is only precluded when HMW hyaluronan is processed to a LMW form by a specific hyaluronidase (PH20) that is present in OPCs and astrocytes in lysolecithin-induced lesions and MS lesions (Back et al., 2005; Preston et al., 2013). Hence, digestion products of HMW hyaluronan as well as unprocessed LMW hyaluronan likely prevent OPC maturation in chronic MS lesions, thereby contributing to remyelination failure (Figure 2; Preston et al., 2013).

Collagens are trimeric proteins containing long triple helical sequences that have the ability to form stable fibrils. They are arranged into networks and are involved in structuring and providing rigidity to the ECM. In the adult CNS, collagen is mainly limited to the basement membranes (e.g., collagen IV) and is hardly present in the interstitial matrix, which makes the brain a relatively soft tissue. While fibrillar collagens are not present in CNS parenchyma upon cuprizone-induced demyelination (Hibbitts et al., 2012), fibrillar collagen V is closely associated with astrocytes in the interstitial matrix of active MS lesions (Mohan et al., 2010). Furthermore, genes involved in collagen synthesis are highly expressed in the rim of inactive MS lesions (Hendrickx et al., 2017). Also, the accumulation of fibrillary

collagens I and II is associated with perivascular inflammation in the center of active and mixed active/inactive MS lesions, and mainly restricted to basement membranes, playing a role in limiting the enlargement of MS lesions (Mohan et al., 2010). MS proteome analyses demonstrated an enrichment of collagen IV, primarily localizing in the basement membranes in inactive lesions (Satoh et al., 2009). Although OPCs lack collagen-recognizing integrins, OPC migration is inhibited on collagen I substrates (Milner, Edwards, Streuli, & ffrench-Constant, 1996), and collagen I microspheres support OPC differentiation (Yao, Phan, & Li, 2013). Therefore, the contribution of interstitial collagen to remyelination failure via direct modulation of OPC behavior in MS lesions is likely negligible.

3.2 | Fibrous ECM glycoproteins

Fibronectins are high-molecular weight glycoproteins that are produced by a single gene (Hynes & Yamada, 1982; Pankov & Yamada, 2002). There are two types of fibronectin: plasma fibronectin and cellular fibronectin. Plasma fibronectin is a soluble compound that is generated by hepatocytes and circulates in the periphery (Owens & Cimino, 1982). Cellular fibronectin is insoluble and locally produced; in the CNS it is deposited by astrocytes, microglia/macrophage, and endothelial cells (Hibbitts et al., 2012; Stoffels et al., 2013; Zhao, Fancy, Franklin, & ffrench-Constant, 2009). In normal healthy adult CNS, fibronectin is nearly absent in the interstitial ECM and only localizes to the vasculature (Sobel & Mitchell, 1989; Stoffels et al., 2013; van Horssen, Bo, Vos, Virtanen, & de Vries, 2005; Zhao, Fancy, Franklin, & ffrench-Constant, 2009). Fibronectin is a major component of the transient ECM in various tissues upon injury guiding tissue repair, where it binds many other ECM components to form matrices. In this manner, it regulates cell behavior via integrin receptors, in particular cell migration and proliferation (Pankov & Yamada, 2002; Singh, Carraher, & Schwarzbauer, 2010). Also, in various experimental toxin-induced lesions undergoing efficient remyelination, fibronectin is transiently expressed in white matter CNS parenchyma and upregulated in the vasculature and its level declines as remyelination proceeds (Espitia Pinzon et al., 2017; Hibbitts et al., 2012; Stoffels et al., 2013; Zhao et al., 2009). In active, mixed active/inactive and inactive white matter MS lesions, however, the increased vascular and extracellular fibronectin expression persists, and the protein is present in perivascular infiltrates (Sobel & Mitchell, 1989; Stoffels et al., 2013; van Horssen et al., 2005). In addition, fibronectin is associated with inflammation-mediated aggregation in chronic lesions (Stoffels et al., 2013). Fibronectin expression is still increased in remyelinated shadow plaques, but does not aggregate (Stoffels et al., 2013). Astrocytes are the predominant source of cellular fibronectin upon lysolecithin-induced demyelination (Stoffels, Hoekstra, Franklin, Baron, & Zhao, 2015), while in MS lesions fibronectin levels increase within demyelinated regions by both leakage from the blood circulation and production by reactive astrocytes (Sobel & Mitchell, 1989; Stoffels et al., 2013; van Horssen et al., 2005). Interestingly, white

matter astrocytes isolated from postmortem MS brain tissue show enhanced fibronectin aggregation compared to normal astrocytes that mainly deposit dimeric fibronectin (Stoffels et al., 2013). *In vitro*, dimeric fibronectin mediates OPC migration and proliferation (Baron, Shattil, & ffrench-Constant, 2002; Frost, Kiernan, Faissner, & ffrench-Constant, 1996; Milner et al., 1996; Stoffels et al., 2013; Tripathi, Parikh, Vora, Frost, & Pillai, 2017), while fibronectin coatings prevent myelin membrane formation, likely by perturbing (secondary) process outgrowth, myelin-directed vesicle transport, and formation of functional membrane microdomains (Baron et al., 2014; Buttery & ffrench-Constant, 1999; Lafrenaye & Fuss, 2010; Maier et al., 2005; Siskova, Baron, de Vries, & Hoekstra, 2006; Siskova et al., 2009; Stoffels et al., 2013). Similar to dimeric fibronectin, aggregates of fibronectin inhibit myelin membrane formation and myelination in mono- and co-culture systems (Qin et al., 2017; Stoffels et al., 2013). Thus, upon CNS white matter demyelination, transient expression of fibronectin precedes successful remyelination, and may be beneficial in OPC recruitment, whereas the pathological fibronectin aggregates impair remyelination in MS lesions (Figure 2).

Vitronectin is another glycoprotein that is mainly localized in the vasculature of the adult CNS. The expression of microglia/macrophages-derived vitronectin is transiently enhanced upon ethidium bromide-induced demyelination (Zhao et al., 2009). In MS, vitronectin is deposited in active lesions and at the edges of mixed active/inactive demyelinating lesions, where it is localized on the microvasculature, on demyelinated axons, and is present in a subset of hypertrophic astrocytes (Sobel, Chen, Maeda, & Hinojoza, 1995). Next to localized synthesis, part of the vitronectin acquires access into the brain, following passage across the disrupted BBB (Sobel et al., 1995). Vitronectin is absent in inactive lesions (Sobel et al., 1995). It promotes migration and proliferation of cultured OPCs (Baron, Shattil, & ffrench-Constant, 2002; Frost, Kiernan, Faissner, & ffrench-Constant, 1996), indicating that vitronectin may regulate OPC recruitment, and that the absence of the compound in chronic lesions may contribute to the reduced number of OPCs in white matter MS lesions.

Laminins are self-polymerized and heterotrimeric glycoproteins that serve as major adhesive proteins in basement membranes. Multiple genes code laminin subunits, known as α , β , and γ polypeptide chains that assemble into distinct laminin variants (Colognato & Yurchenco, 2000). In the healthy adult CNS, laminins are predominantly found at the vascular endothelial (mainly laminin-5, -8, and -10) and astroglial (mainly laminin-1 and -2) basement membranes (Sixt et al., 2001; van Horssen et al., 2005; Zhao et al., 2009). Upon CNS development, laminin-2 is localized to axons where it promotes the maturation of OPCs into oligodendrocytes, OPC proliferation, survival of oligodendrocytes, and myelination (Colognato et al., 2002; Colognato & Tzvetanova, 2011; Frost, Buttery, Milner, & ffrench-Constant, 1999; Leiton et al., 2015; Relucio, Tzvetanova, Ao, Lindquist, & Colognato, 2009; Relvas et al., 2001). Laminin-2 expression is upregulated upon CNS white matter demyelination and appears around axons at a time point that coincides with the onset

of myelin membrane formation (Zhao et al., 2009), and may thus promote remyelination. In active and chronic MS lesions, the expression of laminin is mainly enhanced at the vascular and not in the lesion parenchyma (Esiri & Morris, 1991; Sobel, Hinojoza, Maeda, & Chen, 1998; van Horssen et al., 2005), indicating that beneficial effects of laminin on oligodendrocyte behavior and remyelination may be negated in MS.

3.3 | Matricellular proteins

Matricellular proteins are non-structural regulators of the ECM that contain binding sites for other ECM proteins as well as cell surface receptors, and therefore play important roles in controlling cell behavior and ECM remodeling (Bornstein & Sage, 2002). Tenascin-C and tenascin-R are large hexameric and trimeric glycoproteins, respectively, assembled from monomers via disulfide bridges (Erickson & Inglesias, 1984; Norenberg, Hubert, & Rathjen, 1996). The proteins are expressed in the normal adult CNS (Bartsch et al., 1992; Garcion, Faissner, & ffrench-Constant, 2001; Gutowski, Newcombe, & Cuzner, 1999) and bind to CSPGs, hyaluronan, and fibronectin (Chiquet-Ehrismann, 1991, 2004; Midwood, Chiquet, Tucker, & Orend, 2016). The expression of tenascin-R is specific to the CNS and produced by oligodendrocytes, as well by neurons during development (Fuss, Wintergerst, Bartsch, & Schachner, 1993; Pesheva, Spiess, & Schachner, 1989), while tenascin-C is a more ubiquitous ECM protein (Midwood et al., 2016). In the CNS, tenascin-C is expressed by astrocytes and oligodendrocytes (Bartsch et al., 1992; Czopka, Von Holst, Schmidt, ffrench-Constant, & Faissner, 2009; Garwood et al., 2004; Gotz, Bolz, Joester, & Faissner, 1997; Gutowski et al., 1999; Prieto, Jones, Cunningham, Crossin, & Edelman, 1990). Upon ethidium bromide-induced demyelination, both tenascin-C and tenascin-R are upregulated and produced by reactive astrocytes and recruited OPCs, respectively (Zhao et al., 2009). While tenascin-C and tenascin-R are enhanced at the gene expression level upon cuprizone-induced demyelination in one study (Zendedel et al., 2016), another study shows that tenascin-C mRNA is not strongly upregulated (Hibbitts et al., 2012). In active MS lesions, both tenascin-C and tenascin-R are significantly downregulated, extending even beyond the edge of the lesion, that is at NAWM areas where the presence of macrophages is abundant (Gutowski et al., 1999). In the center of inactive MS lesions, the levels of tenascin-C and tenascin-R are almost similar to NAWM, while being reduced at the lesion rim (Gutowski et al., 1999). While tenascin-C mRNA levels are upregulated in inactive lesions compared to NAWM (Zeis, Howell, Reynolds, & Schaeren-Wiemers, 2018), tenascin-C and tenascin-R protein levels in active lesions resemble adjacent NAWM (Gutowski et al., 1999). Reactive astrocytes are likely the main producers of both tenascins in chronic lesions. Tenascin-R coatings function as a stimulator of OPC differentiation and upregulate myelin proteins (Czopka, Von Holst, Schmidt, ffrench-Constant, & Faissner, 2009; Pesheva, Gloor, Schachner, & Probstmeier, 1997), while at least *in vitro* the formation of myelin

membranes is retarded (Czopka et al., 2009). Tenascin-C inhibits OPC migration (Frost et al., 1996; Garcion, Faissner, & ffrench-Constant, 2001; Kiernan, Gotz, Faissner, & ffrench-Constant, 1996) as well as differentiation and myelin membrane formation (Czopka, von Holst, ffrench-Constant, & Faissner, 2010; Czopka et al., 2009; Garwood et al., 2004), while promoting OPC proliferation (Garcion et al., 2001) and survival (Garwood et al., 2004). Oligodendroglial contactin is involved in the tenascin-C-mediated inhibition of OPC differentiation (Czopka, von Holst, ffrench-Constant, & Faissner, 2010). Thus, while its degradation in active MS lesions may initially benefit OPC migration, premature re-expression by reactive astrocytes in chronic lesions may maintain OPCs in an immature state.

Thrombospondin-1 is a trimeric matricellular protein that is present in the adult CNS (Asch, Leung, Shapiro, & Nachman, 1986), expressed by astrocytes (Scott-Drew & ffrench-Constant, 1997) and involved in CNS synaptogenesis (Christopherson et al., 2005; Risher & Eroglu, 2012). Upon ethidium bromide-induced demyelination, thrombospondin-1 mRNA and protein are slightly upregulated at early demyelination (Zhao et al., 2009). Immunohistochemical analysis of thrombospondin in MS lesions has not been reported thus far. However, thrombospondin-1 mRNA levels are increased in active and inactive MS lesions (Mohan et al., 2010), while thrombospondin-1 protein levels are enriched in mixed active/inactive and inactive MS lesions (Satoh et al., 2009; Sikkema et al., 2018). Also, thrombospondin binds to fibronectin (aggregates) and collagen V (Adams & Lawler, 2011; Aho & Uitto, 1998; Sikkema et al., 2018), which are present in the interstitial ECM of MS lesions. *In vitro*, thrombospondin-1 coatings promote migration of an OPC-like cell line (Scott-Drew & ffrench-Constant, 1997), indicating that thrombospondin-1 may be involved in OPC recruitment.

Osteopontin is a secreted matricellular protein that binds directly to fibronectin and collagen (Giachelli & Steitz, 2000), and is expressed in grey but not in white matter in the normal adult CNS (Selvaraju et al., 2004; Shin, Cha, Chun, Chung, & Lee, 1999; Zhao, Fancy, ffrench-Constant, & Franklin, 2008). However, the protein is transiently upregulated in white matter upon cuprizone- (Selvaraju et al., 2004) and ethidium bromide-induced (Zhao, Fancy, ffrench-Constant, & Franklin, 2008) demyelination. Microglia/macrophages and astrocytes show osteopontin immune reactivity (Selvaraju et al., 2004; Zhao et al., 2008), while only microglia/macrophages harbor osteopontin mRNA (Zhao et al., 2008), and likely secrete osteopontin in the demyelinated areas. Microarray analyses showed that osteopontin mRNA levels are higher in active MS lesions than in control white matter (Chabas et al., 2001). In addition, proteomic analyses revealed that osteopontin protein is enriched in mixed active/inactive MS lesions compared to control white matter and inactive MS lesions (Satoh et al., 2009). Within active MS lesions, osteopontin is mainly present in macrophages and microvasculature endothelial cells, while reactive astrocytes also express osteopontin in active and mixed active/inactive MS lesions (Diaz-Sanchez, Williams, DeLuca, & Esiri, 2006; Sinclair, Mirakhur, Kirk, Farrell, & McQuaid, 2005). Moreover, osteopontin is also present in astrocytes in NAWM at areas with high levels of

microglia activation (Chabas et al., 2001; Sinclair et al., 2005) and occasionally in white matter oligodendrocytes (Chabas et al., 2001; Diaz-Sanchez et al., 2006). Contrastingly, while protein levels are increased, gene expression analysis of adjacent NAWM, rim and center of mixed active/inactive and inactive lesions revealed a downregulation in osteopontin transcript levels (Koning, Bo, Hoek, & Huitinga, 2007). *In vitro* studies demonstrated that *soluble* osteopontin induces proliferation in OPC-like cell lines and increases the expression of myelin basic protein (MBP) and myelin membrane formation in mixed cortical cultures (Selvaraju et al., 2004). Although proliferation and differentiation are seemingly opposite processes, both are necessary for successful remyelination. Similar to an integrin- and developmental stage-dependent switch in growth factor signaling (Baron, Colognato, & ffrench-Constant, 2005; Baron et al., 2002; Colognato et al., 2002), the effect of osteopontin on OPC behavior may depend on the developmental stage and to which integrin it binds. Thus, osteopontin may mediate OPC proliferation via integrin $\alpha\beta3$, whereas OPC differentiation may be induced by signaling via integrin $\alpha\beta5$ (Blaschuk, Frost, & ffrench-Constant, 2000). In favor of a developmental stage-dependent effect is that osteopontin is added to differentiating mixed cortical cultures (Selvaraju et al., 2004), that is when OPC proliferation is ceased. Alternatively, in mixed cultures the effect of osteopontin on OPC differentiation may be indirect. Hence, osteopontin may be beneficial to remyelination at both OPC recruitment and OPC differentiation levels (Figure 2).

The involvement of other matricellular proteins, including CCNs, SPARC, and fibulins in ECM remodeling upon demyelination and in remyelination failure in MS, remains to be determined. Of interest is that Cyr61/CCN1 and CTGF/CCN2 associate with fibronectin aggregates (Sikkema et al., 2018), and that CTGF/CCN2 inhibits OPC differentiation (Ercan et al., 2017; Lamond & Barnett, 2013), adding another level of complexity to fibronectin aggregate-mediated perturbation of OPC maturation. In addition, regulatory T cell-derived NOV/CCN3 promotes oligodendrocyte and myelination in demyelinated toxin-induced lesions, although it is not clear whether CCN3 acts directly on cells of the oligodendrocyte lineage or via other cells (de la Vega Gallardo, Dittmer, Dombrowski, & Fitzgerald, 2018; Dombrowski et al., 2017).

4 | DISTURBED ECM EXPRESSION IN MS LESIONS

When comparing the expression pattern of ECM molecules in the distinct MS lesions with the expression pattern of ECM molecules that are altered upon successful CNS remyelination in rodents both similarities and abnormalities are noticed (Table 1, Figure 1). In addition, inter- and intralesional heterogeneity in the localization of ECM proteins in the distinct white matter lesions is apparent. Why the expression of ECM proteins in MS lesions is abnormal, whether this affects remyelination, and what contributes to ECM heterogeneity in MS lesions are reviewed next.

4.1 | Role of abnormal ECM in remyelination failure

Similar to demyelinating CNS white matter injury in experimental models, ECM molecules that are absent in the healthy adult CNS are upregulated upon demyelination in MS lesions, indicating a “normal” initial response to demyelination in MS lesions. These interstitial ECM proteins in general contribute to OPC migration and proliferation (Figure 2), and prevent premature OPC differentiation. In experimental models where remyelination is successful, the proteins are transiently expressed and cleared at the onset of remyelination to allow for OPC differentiation, among others by the increased expression of laminin (Zhao et al., 2008). In MS lesions, the initial transient increased ECM proteins persist, while the remyelination beneficial ECM protein laminin is virtually absent in the interstitial ECM MS. This indicates that the “normal” ECM remodeling response in MS lesions is derailed and not converted to a “remyelination-favoring mode” (Table 1 and Figure 1). Another striking difference is that CSPGs, present in the interstitial ECM CNS, are upregulated upon demyelination in experimental toxin-induced demyelination rodent models, and downregulated at the center of white matter MS lesions. As CSPGs are present inside phagocytic macrophages in the center of active lesions (Sobel & Ahmed, 2001), CSPGs may be initially deposited in active MS lesions and cleared by macrophages (Sobel & Ahmed, 2001). Whether the absence of CSPGs in inactive lesions is also the result of active clearance remains to be determined. CSPG proteins are merely inhibitory for OPC recruitment and differentiation (Figure 2), which in healthy CNS may keep the adult OPCs at their location in an immature state. Therefore, their transient degradation may be beneficial to remyelination. However, these ECM proteins are upregulated and not downregulated upon demyelination in experimental models, although their expressions at early time points, that is immediately upon induction of demyelination, have not been reported thus far. Intriguingly, with regard to ECM expression, the edges of active and mixed active/inactive MS lesions resemble demyelinated areas in experimental models more than the core of MS lesions, with the exception of tenascins (Table 1 and Figure 1). Indeed, remyelination at the rim is more pronounced than that at the MS lesion center (Raine & Wu, 1993), suggesting that the interstitial ECM at the edges of active and mixed active/inactive lesions is more permissive for remyelination than the ECM in the center of the lesions. However, the degree of remyelination depends on the *net* ratio of myelination-supportive (e.g., laminin) and myelination-inhibitory ECM molecules (e.g., fibronectin aggregates, hyaluronan, CSPGs). *In vitro*, fibronectin-derived inhibitory signals dominate over myelination-promoting laminin signals (Baron et al., 2014), while only very high amounts of laminin can overcome the inhibitory effect of CSPGs on OPC differentiation (Lau et al., 2012; Sun et al., 2017). In fact, in some studies, the effect of CSPGs on OPC behavior have been performed on a relative high laminin background (Pendleton et al., 2013; Siebert & Osterhout, 2011), further indicating that CSPGs are likely dominant over laminin. Thus, given that aggregates of fibronectin accumulate in chronic MS lesions and CSPGs at the edge of (chronic) active MS lesions, these remyelination-inhibiting obstacles have to be removed or their effects have to be bypassed to enable regeneration of myelin.

4.2 | Role of glial scar and inflammation

Astrocytes, microglia, and macrophages are the producers of ECM proteins in MS lesions. The astrocyte response in MS lesions is of dual nature, that is both astrocyte loss and astrogliosis are associated with remyelination failure (Correale & Farez, 2015; Nair, Frederick, & Miller, 2008; Williams et al., 2007). Major barriers that contribute to remyelination failure in MS are glial scars, that is astrogliosis, which parallels ECM alterations, and the ensuing inflammation. The changes in reactive astrogliosis are regulated in a context-specific manner (Sofroniew & Vinters, 2010), and given that the distinct cellular composition between the edge and center of, for example, mixed active/inactive MS lesions, this may result in a different signaling environment and different extent of gliosis, and hence differences in ECM composition. Indeed, in MS lesions, antigenic differences that reflect the state of reactive astrocytes, that is between astrocytes at the lesion edge and center, exist (Holley, Gveric, Newcombe, Cuzner, & Gutowski, 2003; Park et al., 2019), indicating that at least two distinct glial scars are formed. The glial scar around the lesions is formed as a neuroprotective response to disruption of the BBB, and mainly prevents further expansion of the lesion (Nair et al., 2008). If so, it is tempting to suggest that the glial scar formed within the lesion center is a result of the fact that the required cells for tissue repair, that is cells that express the appropriate proteases that clear the transient ECM, could not reach the lesion site. Indeed, the edge of active and inactive MS lesions is mainly composed of CSPGs (Table 1 and Figure 1) that prevent the entry of inflammatory cells, including lymphocytes and macrophages in chronic MS lesions.

Thus, the different responses of astrocytes likely result in different reactive phenotypes that are present in the distinct MS lesions (John et al., 2002; Nair et al., 2008), which may account for the distinct interlesional and intralesional local ECM profile. Major contributors to the formation of glial scars are inflammatory mediators, such as IL-1 β , IL-10, TNF α , IFN γ , and TGF β , as well as endogenous TLR ligands (Asher et al., 2000; John et al., 2004; John, Lee, & Brosnan, 2003; John, Lee, Song, Riviello, & Brosnan, 2005; Sofroniew & Vinters, 2010). Importantly, the different levels and distinct composition of inflammatory cues are present in the distinct lesions and at the borders of expanding active MS lesions (Cannella & Raine, 1995; Koning et al., 2007; Woodroffe, Bellamy, Feldmann, Davison, & Cuzner, 1986). A glial scar barrier is absent in cuprizone-induced demyelination models, where inflammation does not play a major role (Hibbitts et al., 2012), while removing the toxin leads to the clearance of ECM molecules and enables remyelination. In contrast, glial scars are formed in immune-mediated demyelination models such as experimental autoimmune encephalomyelitis (EAE) and Theiler's murine encephalomyelitis (TME) that more closely resemble the situation in MS, including an inflammatory environment, and where remyelination is insufficient (Haist, Ulrich, Kalkuhl, Deschl, & Baumgartner, 2012; Smith & Eng, 1987). For example, similar to MS lesions, in chronic relapsing EAE but not upon toxin-induced demyelination, astrocyte-derived HMW hyaluronan (Back et al., 2005) and fibronectin aggregates

(Stoffels et al., 2013) accumulate in lesioned areas. Also, CSPG proteins neurocan, aggrecan, brevican, and versican V1 are also increased at the peak of clinical EAE severity, whereas the expression of versican V2 is reduced (Sajad, Zargan, Chawla, Umar, & Khan, 2011; Stephenson et al., 2018). Aggrecan is only present in spinal cord grey matter, while versican V1 is also present in perivascular cuffs and closely associated with infiltrating immune cells (Sobel & Ahmed, 2001). In TME, which is characterized by mild inflammation and insufficient OPC differentiation (Ulrich, Seeliger, Kreutzer, Germann, & Baumgartner, 2008), ECM alterations correlated with the development of astrogliosis and include among other intralesional deposition of laminin, tenascin-C, neurocan, and fibronectin, while phosphacan expression decreases and aggrecan expression remains similar (Haist et al., 2012).

Next to reactive astrocytes, other major cellular components that contribute to the dysregulated remodeling of the ECM in MS lesions are the resident microglia and the infiltrating macrophages. Microglia and macrophages are actively remodeling the ECM being producers of ECM proteins and of MMPs, that is proteases that are able to degrade and remodel the ECM (Lloyd & Miron, 2019). Given the complex beneficial and detrimental roles of microglia and macrophages in remyelination (Lloyd & Miron, 2019), and their mixed phenotype in MS

lesions (Miron et al., 2013; Peferoen et al., 2015; Vogel et al., 2013), the persistent or incorrect expression of ECM molecules in MS lesions might result from altered expression patterns of microglia/macrophage-derived MMPs (Kieseier et al., 1999), which is discussed next.

5 | MMPs UPON DEMYELINATING INJURY

MMPs are a family of proteolytic enzymes, also referred to as endopeptidases, that are essential for ECM remodeling in many processes. These include migration, wound healing, tissue morphogenesis, cell differentiation, neuronal growth, and several signaling processes (Lu et al., 2011; Page-McCaw et al., 2007). This family consists of 26 members, of which 24 are present in mammalian, divided into six subgroups: collagenases (MMP1, MMP8, MMP13), gelatinases (MMP2, MMP9), stromelysins (MMP3, MMP10, MMP11), matrilysins (MMP7, MMP26), membrane type (MT)-MMPs (MMP14, MMP15, MMP16, MMP17, MMP24, MMP25), and other MMPs. All newly synthesized MMPs contain a signal peptide that is cleaved during transport via the secretory pathway. There are small differences in the structure of the MMPs, but three common domains are identified (Figure 3; Page-McCaw et al., 2007).

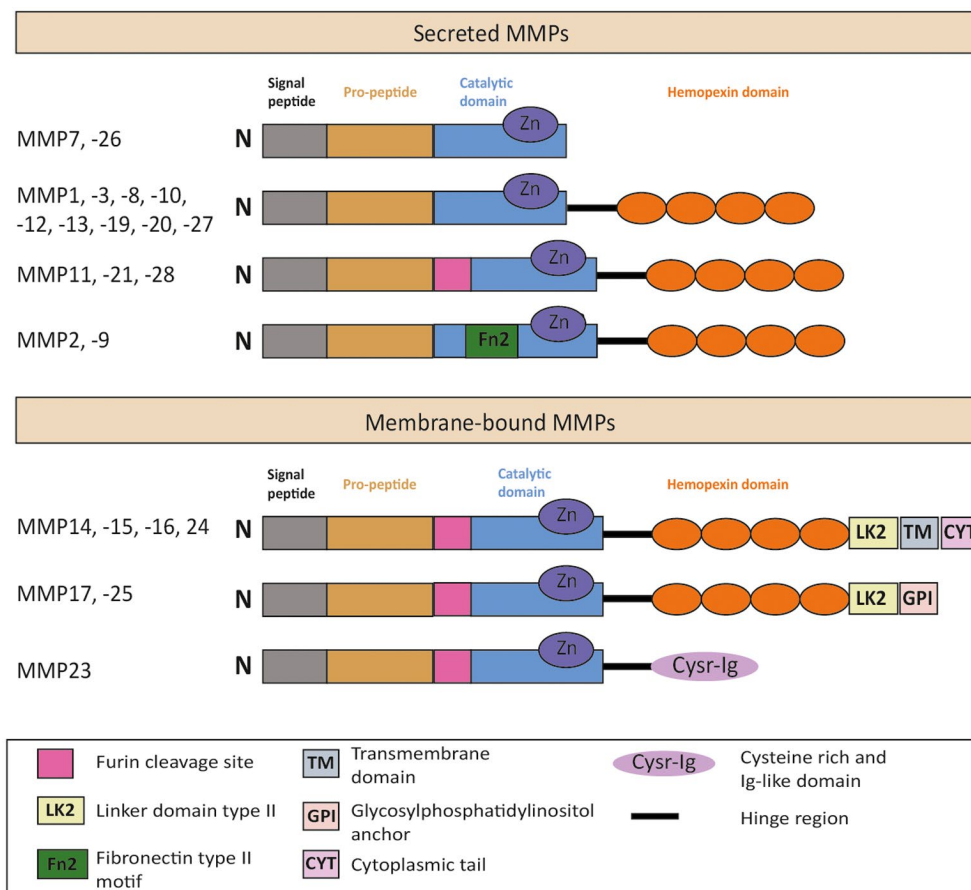


FIGURE 3 Schematic structure of the matrix metalloproteinase family. Matrix metalloproteinases (MMPs) share a conserved domain structure of a N-terminal pro-peptide and catalytic domain and a C-terminal hemopexin domain that is connected via a hinge region. MMPs are secreted or are membrane type (MT-MMPs) that are linked to the plasma membrane via transmembrane domain or by a GPI anchor

A propeptide region is located at the N terminus of the protein, which prevents proteolytic activity through interaction with the catalytic domain. This domain is removed to activate the enzyme. The catalytic domain is also located at the N terminus, in which a zinc-binding motif is inserted. The catalytic domain of gelatinases contains an additional domain, called fibronectin type II-like domain. Except for matrilysins, the C-terminal part of MMPs contains a haemopexin-like domain, which is involved in substrate recognition and anchoring, and interacts with the catalytic domain via a hinge region. The membrane type-MMPs (MT-MMPs) are membrane proteins, whereas all other MMPs are secreted into the extracellular space. Here, they are able, however, to localize at the cell surface by binding to MT-MMPs and other cell surface molecules. MMPs have overlapping substrates, and in addition these enzymes are jointly capable of degrading virtually all ECM proteins. MMPs play also a crucial role in the shedding of growth factors, cytokines, chemokines, receptors, cell-adhesion molecules, and activation of other MMPs (Page-McCaw et al., 2007). Obviously, given this diversity, the activity of MMPs is tightly regulated. For expression, cells have to be activated for transcription of MMPs. The secreted forms require cleavage of the propeptide for activation, while MMP activity can be inhibited by tissue inhibitors of metalloproteinases (TIMPs; Lu et al., 2011; Page-McCaw et al., 2007).

In the healthy adult CNS, MMP activity is crucial in supporting cognitive processes, such as learning and memory, due to ECM remodeling and the regulation of synaptic plasticity and long-term potentiation (Agrawal, Lau, & Yong, 2008; Huntley, 2012). Also, the physiology of axons, myelin turnover, and angiogenesis are regulated

by several MMPs. In addition, differential expression of MMPs in the development of the CNS is essential for neurogenesis and axonal growth as well as for the function of oligodendrocytes and myelinogenesis. MMPs also play important roles in repair processes and in pathology, and both beneficial and detrimental functions have been assigned to MMPs in the injured CNS (Javaid, Abdallah, Ahmed, & Sheikh, 2013; Yong, 2005; Yong, Power, Forsyth, & Edwards, 2001). To remodel the ECM, demyelination and subsequent remyelination require a transient alteration in the expression pattern of MMPs. In addition, MMPs may affect OPC behavior by modulating the bioavailability of several proteins, including growth factors and cytokines (Dubois-Dalcq & Murray, 2000; McCawley & Matrisian, 2001). However, uncontrolled and abundant expression of MMPs may damage the BBB, induce inflammation, and neurotoxicity, which may lead to (demyelinating) injury (Agrawal et al., 2008; Yong, 2005; Yong et al., 2001). Of interest, synergism among MMP2, MMP9, and MMP7 genes may be a susceptibility factor for MS (Rahimi et al., 2016). In the following, we provide an overview of current insight into the role of distinct MMPs in successful remyelination and their expression in the distinct MS white matter lesions (summarized in Table 2 and Figure 1). Also, the consequence for demyelinating pathology is discussed.

5.1 | MMP3

Škuljec et al. (2011) investigated the expression profile of eleven MMPs (MMP2, MMP3, MMP7, MMP9, MMP10, MMP11, MMP12, MMP13, MMP14, MMP15, and MMP24) upon cuprizone-induced

TABLE 2 Expression of MMPs upon toxin-induced demyelination and in distinct white matter MS lesions and their MS relevant ECM targets

MMP	MS relevant ECM targets	Experimental rodent models		Multiple sclerosis		
		Demyelination	Remyelination	Active	Mixed active/inactive	Inactive
MMP2	Aggrecan, versican, neurocan, collagen V, fibronectin, laminin, vitronectin, tenascin-C (large)	=	=	↑ ^a	↑ ^a	=
MMP3	Aggrecan, versican, neurocan, phosphacan, collagen V, fibronectin, laminin, vitronectin, tenascin-C (large), osteopontin	↑	↑	↑	↑ ^b	=
MMP7	Aggrecan, fibronectin, laminin, vitronectin, tenascin-C (large, small), osteopontin	=	↑	↑ ^a	↓ ^b	↓ ^b
MMP9	Aggrecan, collagen V, fibronectin, vitronectin, osteopontin	=	↑	↑	↑ ^a	=
MMP12	Aggrecan, fibronectin, laminin, vitronectin, osteopontin	↑	↑	↑	↑ ^a	=
MMP19	Aggrecan, fibronectin, laminin, tenascin-C (large)	n.d.	n.d.	↑	↑ ^a	=

Note: Increased (↑), decreased (↓), and similar (=) expression compared to control.

Abbreviation: n.d., not determined.

^aMarked expression at the edge.

^bAlso based on biochemical analysis (Wang et al., 2018).

demyelination and subsequent remyelination. At early demyelination, MMP3 mRNA is upregulated, followed by a return to normal levels during late stages of demyelination. A second more prominent upregulation of MMP3 mRNA is observed upon remyelination, which is also reflected at the protein level (Skuljec et al., 2011; Wang et al., 2018). MMP3 mRNA levels, but not protein levels, are also increased upon early remyelination in the lysolecithin-induced demyelination model (Wang et al., 2018). At the protein level, MMP3, also referred to as stromelysin-1, is predominantly expressed by astrocytes, but may also be produced by damaged neurons, microglia, and oligodendrocytes following other types of CNS injury (Van Hove, Lemmens, Van de Velde, Verslegers, & Moons, 2012). An (early) upregulation of MMP3 is also observed in the inflammatory TME model (Hansmann et al., 2012; Ulrich et al., 2006), and in EAE (Weaver et al., 2005). In these inflammatory models with insufficient remyelination, MMP3 may aid to the disruption of the BBB. In addition, the early upregulation of MMP3 may cause the breakdown of myelin and exacerbate demyelination (Chandler, Cossins, Lury, & Wells, 1996; Shiryayev et al., 2009). In contrast, the upregulation of MMP3, observed at remyelination in the toxin-induced models, may facilitate myelin regeneration. MMP3 modulates several signaling pathways, such as the bioavailability of some soluble growth factors, including IGF-1, that facilitate oligodendrocyte differentiation and myelin production (D'Ercole, Ye, & O'Kusky, 2002; Dubois-Dalcq & Murray, 2000; Fowlkes et al., 2004; McCawley & Matrisian, 2001; Zeger et al., 2007). In addition, MMP3 degrades several ECM proteins, including CSPGs and fibronectin, and myelin debris, which are components that inhibit differentiation and maturation of oligodendrocytes (Figure 2; Kotter, Li, Zhao, & Franklin, 2006; Lau et al., 2012; Muir et al., 2002; Stoffels et al., 2013; Van Hove, Lemmens, Velde, Verslegers, & Moons, 2012). Hence, MMP3 may be beneficiary of ECM remodeling to facilitate remyelination. MMP3 mRNA is not upregulated in MS lesions compared to white matter of healthy subjects (Lindberg et al., 2001). However, MMP3 protein is present in hypertrophic astrocytes in active and chronic white matter MS lesions, in microglia/macrophages in active lesions and on vasculature in active and mixed active/inactive MS lesions (Maeda & Sobel, 1996; Wang et al., 2018). Biochemical analysis revealed that MMP3 protein levels were increased in mixed active/inactive MS lesions, but not inactive lesions compared to control white matter (Wang et al., 2018). Of interest, MMP3 is a potent activator of other MMPs, such as MMP7 and MMP9 (Lu et al., 2011; Maeda & Sobel, 1996; Van Hove et al., 2012), which are also prominently present in MS lesions (see below).

5.2 | MMP12

The expression level of MMP12, or macrophage elastase, is significantly altered upon cuprizone-induced demyelination. At demyelination, MMP12 mRNA is predominantly produced by microglia/macrophages (Skuljec et al., 2011). In this phase, MMP12 may function in cellular migration of macrophages through ECM remodeling

and degeneration of myelin membranes through cleavage of MBP, one of the major myelin components (Chandler et al., 1996; Gronski et al., 1997; Shipley, Wesselschmidt, Kobayashi, Ley, & Shapiro, 1996). The elevated expression pattern continued during remyelination, where MMP12 is produced by astrocytes and to some extent by oligodendrocytes, rather than microglia/macrophages (Skuljec et al., 2011). Upon remyelination, astrocyte-derived MMP12 may contribute to clearance of both myelin debris and the transiently-expressed ECM proteins, and thus induce a stimulatory environment for remyelination. Also, during CNS development, MMP12 releases IGF-1 from IGF binding protein 6 and is required for process elongation and OPC differentiation (Larsen, DaSilva, Conant, & Yong, 2006; Larsen & Yong, 2004). Studies in EAE and TME models demonstrated an upregulation of MMP12 by microglia/macrophages and a suggested role in disease progression and chronic phases of demyelination, respectively (DaSilva & Yong, 2008; Hansmann et al., 2012; Ulrich et al., 2006). In contrast, the EAE disease course is worse in MMP12 knockout than in wild type mice, which is mediated in part by modulating the Th1/Th2 effector cytokine balance (Weaver et al., 2005) and MMP12-mediated cleavage of osteopontin (Goncalves DaSilva, Liaw, & Yong, 2010). In fact, osteopontin is linked to relapses by enhancing the survival of activated T cells (Hur et al., 2007). This indicates that MMP12 is a protective molecule in EAE. In TME, MMP12 is likely involved in demyelination and extravasation of macrophages, and not in BBB damage or ECM remodeling (Hansmann et al., 2012). In MS lesions, MMP12 protein is present in foamy macrophages and upregulated within active demyelinating lesions, and at the rim of inactive MS lesions and to a lesser extent in the center of mixed active/inactive and inactive lesions (Vos, van Haastert, de Groot, van der Valk, & de Vries, 2003). In contrast to cuprizone-induced demyelination, in MS lesions, MMP12 is not observed in astrocytes and oligodendrocytes. Hence, the predominant macrophage expression of MMP12 in active demyelinating MS lesions may have a dual role with regard to demyelination, that is it may induce death of activated T cells by cleaving osteopontin, but may also induce bystander demyelination by cleaving MBP. Notably, MMP12 is present at lower levels in cerebrospinal fluid (CSF) of MS patients compared to control CSF (Castellazzi et al., 2018).

5.3 | MMP9

MMP9, also called gelatinase B, is one of the most studied MMPs in MS. While MMP9 mRNA expression is unaltered upon cuprizone-induced demyelination compared to unlesioned white matter tissue (Skuljec et al., 2011), MMP9 protein levels are upregulated predominantly in microglia and macrophages at the onset of remyelination upon lysolecithin-induced demyelination (Larsen, Wells, Stallcup, Opdenakker, & Yong, 2003). MMP9 mRNA and protein are upregulated in active and mixed active/inactive demyelinating MS lesions (Anthony et al., 1997; Cossins et al., 1997; Cuzner et al., 1996; Lindberg et al., 2001; Maeda & Sobel, 1996; Mohan et al., 2010). MMP9 mRNA expression is also upregulated in an EAE model

(Clements et al., 1997; Kieseier et al., 1998; Weaver et al., 2005), but not in the TME model (Ulrich et al., 2006, 2008). It is hypothesized that MMP9 is important for the infiltration of inflammatory cells into the CNS. Thus, the level of MMP9 is significantly increased in CSF and serum of MS patients with active disease, compared to healthy individuals (Bar-Or et al., 2003; Benesova et al., 2009; Fainardi et al., 2006; Waubant et al., 1999). Injection of recombinant MMP9 into the CNS parenchyma resulted in breakdown of the BBB, neuronal and myelin loss (Anthony et al., 1998). The localization of MMP9 in cells present in perivascular areas, such as endothelial cells and the infiltrating cell population, including lymphocytes and macrophages, is also in favor of its contribution to the disruption of the BBB in MS (Cossins et al., 1997; Lindberg et al., 2001). In addition, resident CNS cells, such as microglia/macrophages and astrocytes in active MS lesions also express MMP9, mainly around the perivascular areas but also in the CNS parenchyma (Cuzner et al., 1996; Maeda & Sobel, 1996). In mixed active/inactive lesions, MMP9 is more prominently localized at the edge of the lesions (Anthony et al., 1997), while this protease is occasionally also present in astrocytes in inactive lesions. These data further suggest that MMP9 is upregulated and exert its functions in active demyelinating lesions during inflammation. In addition to the stimulation of inflammatory cell infiltration through BBB disruptions, MMP9 derived from leukocytes cleaves MBP and may be involved in the degradation of myelin membranes (Gijbels et al., 1993; Proost, Van Damme, & Opdenakker, 1993). In contrast, MMP9 has also beneficial roles for remyelination (Larsen et al., 2003; Oh et al., 1999; Siskova et al., 2009; Uhm, Dooley, Oh, & Yong, 1998). Localization of MMP9 at the tips of the extending processes of oligodendrocytes is essential for their outgrowth, that is process elongation and arborization is reduced in absence of MMP9 (Oh et al., 1999; Uhm et al., 1998) and upon mislocalization of its activity (Siskova et al., 2009). In addition, MMP9 produced by macrophages and microglia in the remyelination phase degrades NG2, a membrane-spanning CSPG present on OPCs that inhibits maturation of oligodendrocytes (Larsen et al., 2003). Hence, MMP9 plays a dual role in MS. The activity of this enzyme in active demyelinating lesions may be detrimental and contribute to the pathogenesis and progression of MS, but beneficial functions of MMP9 are observed for remyelination, in which it facilitates oligodendrocyte maturation via ECM remodeling.

5.4 | MMP2

MMP2, is another member of the gelatinase family, also referred to as gelatinase A, and is in contrast to MMP3, MMP9, and MMP12, constitutively expressed in the CNS and CSF (Anthony et al., 1997; Rosenberg, 2002). MMP2 mRNA expression is not altered during demyelination and remyelination in a cuprizone-induced demyelination model (Skuljec et al., 2011), and only minor upregulation is observed in EAE (Weaver et al., 2005), in TME (Ulrich et al., 2006) and active MS lesions (Lindberg et al., 2001; Mohan et al., 2010). However, MMP2 protein is present in macrophages and infiltrating cells in

the perivascular area of active MS lesions (Anthony et al., 1997; Diaz-Sanchez et al., 2006; Maeda & Sobel, 1996). MMP2-expressing macrophages are also present at the border of mixed active/inactive lesions, while its expression in chronic lesions is only perivascular (Anthony et al., 1997; Diaz-Sanchez et al., 2006). As MMP9, MMP2 is likely involved in disruption of the BBB (Rosenberg et al., 1992) and has the highest activity in MBP degradation (Chandler et al., 1995; Diaz-Sanchez et al., 2006). MMP2 appears to be more abundant in MS lesions than MMP9, and its expression is predominant in areas of damaged axons, particular at lesion borders (Diaz-Sanchez et al., 2006). Interestingly, MMP2 is also upregulated in NAWM areas adjacent to the lesions (Anthony et al., 1997; Diaz-Sanchez et al., 2006; Maeda & Sobel, 1996). Also, higher levels of MMP2 are present in serum of MS patients (Bar-Or et al., 2003; Benesova et al., 2009). Whether MMP2 may play a role in regeneration of myelin other than its potential to locally degrade only CSPGs, but not laminin, which is present in the same area (Zuo, Ferguson, Hernandez, Stetler-Stevenson, & Muir, 1998), remains to be determined.

5.5 | MMP7

MMP7, also called matrilysin, is constitutively expressed in the brain (Anthony et al., 1997; Wang et al., 2018). However, its mRNA levels are at the lower limit of detection (Clements et al., 1997; Mohan et al., 2010). Given that MMP7 has a potent activity and a broad substrate specificity, it has been suggested that MMP7 may be a regulator of ECM turnover in the healthy brain (Anthony et al., 1997). MMP7 mRNA expression is neither increased upon cuprizone-induced demyelination (Skuljec et al., 2011) nor in the TME (Ulrich et al., 2006) model, while MMP7 mRNA levels were increased upon lysolecithin-induced demyelination, and early remyelination (Wang et al., 2018). In the latter model, MMP7 is localized extracellularly and present in microglia/macrophages (Wang et al., 2018). Contrasting findings are reported in EAE models. In a mouse MOG peptide-induced EAE model MMP7 mRNA levels remain similar (Weaver et al., 2005), while MMP7 mRNA is increased by 500-fold during the course and as protein present in invading macrophages in a MOG-induced rat EAE model (Clements et al., 1997) and increased at the peak of an adoptive-transfer rat EAE model (Kieseier et al., 1998). Also, contrasting findings have been reported for MMP7 mRNA levels in MS lesions: MMP7 mRNA expression is increased in all lesion types in some studies (Cossins et al., 1997; Lindberg et al., 2001), while it was undetectable in active and chronic MS lesions in another study (Mohan et al., 2010). MMP7 protein is localized to parenchymal macrophages and occasionally observed in astrocytes in active MS lesions with a weaker expression in the center than at the edge of the lesion (Cossins et al., 1997; Wang et al., 2018). MMP7 expression in macrophages is also prominent at the lesion borders of mixed active/inactive MS lesions (Anthony et al., 1997) and not as prominent in the center (Cossins et al., 1997), while biochemical analysis reveals that proMMP7 expression is reduced in mixed active/inactive and inactive lesions (Wang et al., 2018). In remyelinated lesions, total

expression levels of MMP7 are comparable to control white matter of healthy subjects with occasional expression in macrophages (Wang et al., 2018). MMP7 is not elevated in serum of MS patients, which is in contrast to MMP9 and MMP2 (Bar-Or et al., 2003). The exact role of MMP7 is not well understood, but like the other MMPs, a role in extravasation of monocytes into the tissue and migration of macrophages through remodeling of basement membrane ECM, such as proteoglycans, fibronectin, laminin, and elastin, can be foreseen. In addition, MMP7 potentially induces bystander demyelination and axonal loss, although likely to a lesser extent than MMP2 and MMP9 (Anthony et al., 1997). However, when expressed in the CNS parenchyma in a timely manner, MMP7 may also be beneficial in clearing the transiently expressed ECM components and myelin debris (Chandler et al., 1995).

5.6 | Other MMPs

Other MMPs that have been analyzed at the protein level in MS lesions are MMP1 (Maeda & Sobel, 1996), MMP19 (van Horssen et al., 2006), and MMP28 (Werner, Dotzlauf, & Smith, 2008). MMP1 is expressed in the majority of macrophages in active MS lesions (Maeda & Sobel, 1996). MMP19 is constitutively expressed by microglia in the healthy adult CNS, and highly expressed in macrophages in the parenchyma and perivascular areas in active MS lesions and in the rim of mixed active/inactive lesions, and occasionally by reactive astrocytes (van Horssen et al., 2006). Also, MMP19 mRNA levels are increased in active and inactive MS lesions (Mohan et al., 2010). While the function of MMP19 in MS pathology remains to be established, it is interesting to note that MMP19 specifically degrades the large isoform of tenascin-C of which the expression is reduced in active MS lesions and mixed active/inactive lesions borders (Table 1 and Figure 1; Stracke et al., 2000). Upregulated MMP28 expression has been shown in one demyelinated, uncharacterized MS lesion, and in EAE (Werner et al., 2008). In addition, MMP28 mRNA is increased in inactive MS lesions (Mohan et al., 2010). Moreover, Western blot analysis also shows a marked upregulation in NAWM compared to control white matter (Werner et al., 2008). In the adult CNS, MMP28 is mainly expressed in neurons and is a negative regulator of myelination (Werner et al., 2008) and macrophage recruitment (Manicone et al., 2009), justifying more research on this protein.

In addition to the marked altered expression patterns of MMP3 and MMP12, several other MMPs, including MT-MMPs, show altered mRNA expression patterns upon cuprizone-induced demyelination (Skuljec et al., 2011). Thus, MMP11 mRNA is upregulated at remyelination, while MMP14 mRNA is upregulated upon both demyelination and remyelination. MMP15 mRNA has been reported to be downregulated at conditions of demyelination, while MMP24 mRNA is downregulated at demyelination but upregulated at remyelination (Skuljec et al., 2011). Mohan et al. (2010) performed an extensive qPCR analysis of 23 MMPs in control white matter, active and inactive MS lesions. In addition to the discussed MMPs, the mRNA levels of MMP11 and MMP14 are more than 2-fold higher in

active lesions than in control white matter and MMP11, MMP14, and MMP17 mRNAs are increased in inactive lesions. In contrast, the mRNA levels of two MMPs (MMP15 and MMP23) and one MMP (MMP23) were downregulated by at least 50% in active and inactive lesions, respectively (Mohan et al., 2010). The cellular localization of these MMPs and their significance for ECM remodeling, remyelination, and MS lesion pathology remains to be determined. Of note, the expression levels of most of these MMPs are also altered in TME and EAE models (Ulrich et al., 2006; Weaver et al., 2005).

6 | MMP DYSFUNCTION IN MS LESIONS

MMPs benefit remyelination by clearing the transiently expressed ECM proteins upon demyelination (Figure 4a). In MS lesions, ECM substrates are not appropriately degraded by MMPs, among others by the absence of MMPs in the lesion center and the inability of MMPs to process substrates at the lesion rim (Figure 4b). In addition, the interference of MMPs with basement membranes contributes to demyelination. In the following, we reflect on MMP dysfunction and how this may contribute to abnormal ECM expression in MS lesions.

6.1 | Altered MMP expression

The expression pattern of MMPs mainly reflects the inflammatory activity of the lesions. In fact, the distribution patterns of MMPs closely resemble each other, mainly localizing in macrophages, often in close association with vasculature, predominantly present in active lesions. Concomitantly, and similar to the intralesional heterogeneity of ECM proteins, a more pronounced expression at the rim of mixed active/inactive MS lesion compared to the core of the lesion is usually observed. Furthermore, MMPs in MS lesions are only occasionally present in astrocytes, with the exception of MMP3, which is primarily localized to astrocytes (Figure 4b). Likely, most MMPs in MS lesions are implicated in disruption of the BBB by affecting its permeability upon enzymatic cleavage of ECM molecules in the basement membrane, such as type IV collagen, fibronectin and laminin, which enables the inflammatory cells, that is lymphocytes and monocytes to infiltrate the CNS (Leppert, Lindberg, Kappos, & Leib, 2001). Also, most MMPs present in inflammatory lesions degrade MBP, which may enhance demyelination and, in turn, contributes to axonal damage (Anthony et al., 1998). However, since MBP is an intracellular, peripheral protein, prior myelin degeneration is obviously required to allow proteolytic accessibility of the protein. In fact, the potential of MMPs to degrade MBP may indirectly facilitate clearance of remyelination-inhibiting myelin debris (Kotter et al., 2006).

Functional *in vivo* evidence for a role MMP-mediated remodeling upon demyelination is currently lacking. Therefore, it is unclear whether the mainly microglia/macrophage-derived MMPs in MS are involved in the dynamic turnover of interstitial ECM upon demyelination. As remyelination fails, among others by the persistent

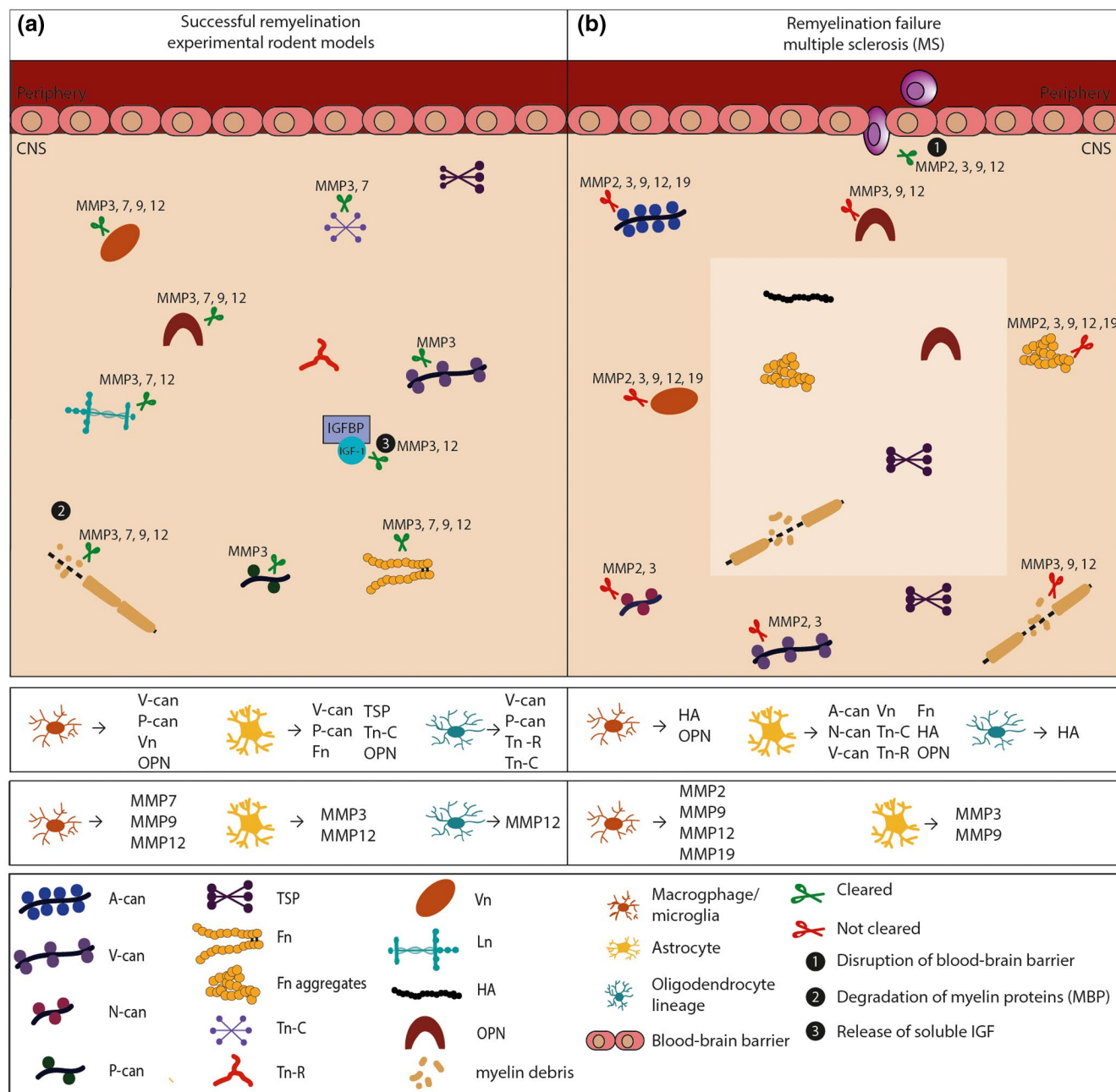


FIGURE 4 Schematic representation of interstitial extracellular matrix (ECM) remodeling upon toxin-induced demyelination in experimental rodent models and in chronic demyelinated MS lesions. Upon demyelination, ECM remodeling, that is transient changes in the expression of ECM proteins and the proteolytic enzymes matrix metalloproteinases (MMPs), regulates oligodendrocyte behavior and thereby remyelination. (a) MMPs and their (ECM) targets in experimental toxin-induced demyelination rodent models of successful remyelination. MMPs are expressed by microglia/macrophages and astrocytes and benefit remyelination by (1) degrading the transiently expressed ECM proteins, (2) clearing myelin debris, and (3) by releasing insulin-like growth factor (IGF) from IGF-binding proteins. (b) MMPs and their (ECM) targets in chronic-demyelinated MS lesions. Note that MS lesions are characterized by intralesional heterogeneity in the expression of MMPs and ECM proteins, that is in the rim and center of the lesion. MMPs are mainly expressed by microglia/macrophages and contribute to demyelination by interfering with blood-brain barrier integrity. In addition, MMPs fail to degrade ECM proteins at the rim of MS lesions, and are absent at the lesion center, resulting in the accumulation of ECM proteins that inhibit oligodendrocyte progenitor cell differentiation. Of relevance, functional *in vivo* evidence for a role of most MMPs in ECM remodeling is currently lacking. Therefore, the indication of their ability to clear (green scissors) or not to clear (red scissors) their targets is based on their presence, their ability to degrade the indicated substrate, and the transient (cleared) or persistent (not cleared) presence of the indicated substrate. Note the distinct cellular expression of MMPs and ECM proteins in experimental rodent models and MS lesions. Thrombospondin-1 expression is increased in chronic demyelinated MS lesions, while data on (cellular) localization are not available. A-can, aggrecan; Fn, fibronectin; HA, hyaluronan; N-can, neurocan; OPN, osteopontin; P-can, phosphocan; Tn-C, tenascin-C; Tn-R, tenascin-R; TSP, thrombospondin-1; V-can, versican; Vn, vitronectin

presence of interstitial ECM components (Table 1, Figures 1 and 2), a dysfunction in MMP expression and/or their activation are more likely relevant parameters in this regard. As discussed above, the composition of both ECM molecules and ECM-degrading MMPs differ between demyelinating injury in experimental rodent models and the distinct white matter MS lesions (summarized in Tables 1 and 2). The tightly and temporal (cellular) expression of several MMPs regulate the clearance of the transiently expressed ECM molecules to enable regeneration of myelin (Figure 4a). In contrast, in MS lesions, where remyelination fails, a different and more persistent pattern of MMPs and ECM molecules is observed (Figure 4b; Agrawal et al., 2008; van Horssen et al., 2007). For example, the mRNA levels of gelatinases MMP2 and MMP9 are not (MMP2) or transiently (MMP9) upregulated upon demyelination and remyelination models (Larsen et al., 2003; Skuljec et al., 2011), but these enzymes are highly expressed in active and mixed active/inactive MS lesions (Anthony et al., 1997; Cossins et al., 1997; Cuzner et al., 1996; Lindberg et al., 2001; Maeda & Sobel, 1996). The disturbed ECM in MS lesions may regulate the expression of these MMPs. Fibronectin increases the expression levels and proteolytic activity of MMP2 and MMP9 by T-lymphocyte cell lines (Esparza et al., 1999). Also, fibronectin and vitronectin induce the expression of MMP9 in microglia (Milner et al., 2007), and trombospondin-1 regulates MMP2 and MMP9 activity (Bein & Simons, 2000; Rodriguez-Manzaneque et al., 2001; Taraboletti et al., 2000) and influences the balance between MMPs and inhibitors (TIMP) in tumor cells (John, Hu, Rothman, & Tuszynski, 2009). Moreover, gelatinases, and MMP9 in particular, are not the most efficient proteases in proteolysis of ECM proteins (Fosang et al., 1992; Imai, Shikata, & Okada, 1995; Muir et al., 2002; Murphy, Cockett, Ward, & Docherty, 1991; Siri et al., 1995). Rather, spatial temporal regulation of MMP2 and MMP9 expression may be more important. Thus, MMP9 cleaves membrane-spanning CSPG NG2, allowing (morphological) oligodendrocyte differentiation (Larsen et al., 2003), while incorrect localization of MMP9, as mediated by fibronectin, perturbs oligodendrocyte process branching (Siskova et al., 2009). Also, MMP2, present at the tips of the axonal extensions, eliminates the CSPG-mediated inhibition of laminin through specific proteolytic cleavage of CSPGs rather than laminin, which is beneficial to regeneration (Zuo et al., 1998). However, MMP2 and MMP9 are also potent inducers of BBB disruption and axonal injury (Anthony et al., 1997; Diaz-Sanchez et al., 2006), and may induce bystander demyelination via degradation of MBP (Chandler et al., 1995). Hence, MMP2 and MMP9 may contribute more to a demyelinating MS pathology than to interstitial ECM remodeling for remyelination.

6.2 | MMPs are present at the rim of chronic MS lesions

MMP7 and MMP3 are more potent proteases to degrade the interstitial ECM, present in MS lesions (Imai et al., 1995; Muir et al., 2002; Murphy et al., 1991; Siri et al., 1995). Therefore, these MMPs are

potentially able to reintroduce a permissive environment for remyelination and improve the neuropathological conditions in MS. Indeed, both MMPs are upregulated at remyelination following demyelination in experimental rodent models (Skuljec et al., 2011; Wang et al., 2018). MMP3 degrades the CSPGs, aggrecan, versican, neurocan, and phosphacan, while MMP7 cleaves aggrecan (Fosang et al., 1992; Muir et al., 2002). However, while CSPG expression is reduced in the center of active MS lesions, where MMP3-expressing astrocytes and MMP7-expressing macrophages are located, there is still accumulation of CSPGs at the lesions borders, where MMP7 expression is more prominent. Therefore, it may be hypothesized that MMP3 and MMP7 are actively degrading CSPGs in the center of active lesions, while these MMPs are not active at the lesion edges. Indeed, immunohistochemistry identifies and spatially localizes MMP, but it does not distinguish active from inactive MMP. Moreover, in MS lesions, most of the MMPs reside within cells and often no extracellular staining is noticed, while for interstitial ECM remodeling MMPs have to be secreted and activated. Activation of MMPs by other proteases is spatially focused and regulated by other MMPs or plasmin, which is locally generated by tissue-type plasminogen activator (t-PA; Lu et al., 2011; Page-McCaw et al., 2007). While absent in control white matter, in MS lesions t-PA is expressed in macrophages and its expression pattern is comparable to MMP expression, that is present in active and absent in chronic lesions (Cuzner et al., 1996). Another tightly regulated mechanism for MMP actions is the regulation of its activity by TIMPs (Lu et al., 2011; Page-McCaw et al., 2007). Upon toxin-induced demyelination, increased mRNA levels of TIMP1 and TIMP2 are observed at demyelination, followed by a gradual decline during remyelination (Skuljec et al., 2011; Wang et al., 2018). TIMP3 is transiently upregulated in the first week during demyelination, whereas TIMP4 is upregulated during remyelination (Skuljec et al., 2011). Lindberg et al. (2001) show that the mRNA levels of these TIMPs are not significantly altered at all MS lesion types. In contrast, Mohan et al. (2010) show that both TIMP1 and TIMP3 mRNA are upregulated in active and inactive lesions, while TIMP3 mRNA are downregulated in inactive lesions. Immunohistochemistry of TIMPs may reveal the expression patterns and cellular localization of TIMPs, and whether the delicate balance between MMP and their inhibitors is disturbed in MS lesions, that is interfere with interstitial ECM remodeling. Also, an *in situ* MMP activity assay on MS lesions may provide insight in localized MMP activity levels. Of note, inhibiting MMP activity reduced the clinical symptoms in an EAE model by reducing the breakdown of the BBB and demyelinating pathology (Gijbels, Galardy, & Steinman, 1994; Liedtke et al., 1998). Hence, although modulation of MMP activity can be an advantageous approach, it remains to be determined whether MMP activity within the CNS is actually inhibited in this model.

In contrast to CSPGs, tenascin expression is reduced in active lesions and the lesion border of inactive lesions, indicating proteolytic activity at these sites. Upon alternative splicing, a large and small isoform of tenascin-C are generated. The small variant is more resistant to degradation, but cleaved by MMP7, while MMP3, MMP7, MMP12, and MMP19 degrade large tenascin-C. Also, other, yet

undefined MMPs, or even non-related proteases, such as cathepsin B (Bever & Garver, 1995; Mai, Sameni, Mikkelsen, & Sloane, 2002), may clear tenascins in active MS lesions and at the border of mixed active/inactive lesions.

6.3 | MMPs are absent in the center of chronic MS lesion

MMPs are hardly present in inactive and in the center of mixed active/inactive lesions, which may be the main reason why the ECM proteins, fibronectin and osteopontin, persist. While loss of function studies demonstrated that fibronectin (Stoffels et al., 2015) and osteopontin (Zhao et al., 2008) are redundant for remyelination, the persistence of otherwise transient ECM proteins in MS lesions, such as fibronectin (aggregates), results in a gain of function, that is they perturb OPC differentiation. Why MMPs are not upregulated in chronic MS lesions is not known. It may be hypothesized that the cellular source of MMPs might determine whether these enzymes perform beneficial or detrimental roles in MS lesions. This is supported by observations that MMP12 is initially produced by microglia/macrophages, while the protease localizes to astrocytes and oligodendrocytes, as observed at successful remyelination, which is beneficial for remyelination. Also, the CSPG-enriched barrier at the lesion border may prevent the migration of cells that produce a suitable MMP to the lesion center. CSPGs are reduced in the lesion center, indicating that they are cleared, but not resynthesized to reestablish the interstitial ECM in adult healthy CNS. Indeed, mRNA levels of CSPGs are reduced in inactive MS lesions (Mohan et al., 2010), which may be due to the lack of sufficient and/or the presence of misactivated microglia/macrophages, the main producers of CSPGs, in the center of lysolecithin-induced lesions (Lau et al., 2012). In this regard, it will be of interest to analyze the ECM composition of remyelinated lesions. In remyelinated lesions, MMP7 levels are comparable to control white matter (Wang et al., 2018), while fibronectin levels are still increased (Stoffels et al., 2013). Of note, astrocyte-derived HMW hyaluronan, which is highly expressed in chronic MS lesions, is degraded by the hyaluronidase family rather than by MMPs (Wang et al., 2018; Wang, Wang, & Li, 2017). Similarly, thrombospondin-1 is also not cleaved by MMPs (Iruela-Arispe, 2008).

7 | CONCLUDING REMARKS AND PERSPECTIVES

Upon demyelinating injury, remodeling of the interstitial ECM is essential in guiding oligodendrocyte behavior to succeed successful remyelination. Remodeling of the interstitial ECM upon demyelination in MS lesions, including the expression patterns of ECM molecules and MMPs, is dependent on the nature of and the localization within lesions, and differs from ECM remodeling upon demyelinating injury in experimental rodent models that show

successful recovery (Figure 4). More specifically, the transient upregulation of ECM proteins, as a natural response to demyelination, persists in MS lesions, among others by dysregulation of MMP expression, their localization and, likely, their activation. Several MMPs are upregulated in a seemingly uncontrollable manner (MMP2 and MMP9), while others (MMP3, MMP7, and MMP12) that perform beneficial functions for remyelination upon demyelination in CNS white matter in rodent models are absent or incorrectly located in MS lesions. Also, and in contrast to demyelination in experimental models, MMPs are mainly expressed by microglia/macrophages and hardly, with the exception of MMP3, by astrocytes (Figure 4). In addition, the phenotype of astrocytes, producers of ECM molecules in the CNS, is changed as a consequence of the ensuing spatially focused inflammation, leading to the formation of at least two glial scars: one at the border of active and inactive lesions, which is enriched in CSPGs, and the other within the center of MS lesions that is devoid of CSPGs, but enriched in fibronectin aggregates, osteopontin, and hyaluronan.

Taking the effect on OPC behavior into account, the persistent presence of mainly OPC differentiation-inhibiting ECM proteins and the absence of myelination-promoting laminin in MS lesions contribute to remyelination failure. As a therapeutic strategy, it is essential to clear or bypass these dominant OPC differentiation-inhibiting ECM proteins, as targeted upregulation of remyelination-promoting laminin may not be efficient to enable regeneration of myelin. Therefore, the ECM environment in MS lesions should also be taken into account when determining the effectiveness of potential remyelination-inducing compounds that are based on stimulating endogenous OPCs or when a cell therapy with exogenous remyelinating cells is considered as a strategy to promote remyelination in MS lesions.

Local activation of MMPs, that is in the rim and/or lesions center with an appropriate substrate specificity, may be a means to degrade ECM depositions and reinstate a permissive environment for remyelination, as is the case in recovery upon demyelination in experimental models. However, the dual role of MMPs, such as their ability to degrade vascular basement membrane ECM components and to induce axonal injury and myelin loss, complicates the development of treatment strategies, aimed at correct interstitial ECM remodeling in favor of remyelination. Thus, MMPs contribute to damage at early lesions stages, while their absence at later stages is detrimental to interstitial ECM remodeling, which, in turn, is essential for the regeneration of myelin. In fact, as microglia/macrophages have also receptors for ECM proteins, the dysregulated interstitial ECM in MS lesions also affects microglia/macrophage activation (Austin et al., 2012; Ebert et al., 2008; Milner et al., 2007; Rolls et al., 2008; Sikkema et al., 2018), which may not only affect MMP expression, but also indirectly contribute to OPC differentiation and therefore remyelination (Lloyd & Miron, 2019; Miron et al., 2013). Hence, means to overcome the dysregulated activation of microglia/macrophages in white matter MS lesions (Peferoen et al., 2015; Vogel et al., 2013) may indirectly also reinstall correct ECM remodeling.

ACKNOWLEDGMENTS

Work in the Baron Laboratory is supported by grants from the Dutch MS Research Foundation (Stichting MS Research, 18-733c MS, J.M.d.J.). P.W. is a recipient of a China Scholarship Council (CSC) fellowship (201306300077).

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

Conceptualization, W.B.; *Writing – Original Draft*, J.M.d.J., P.W., M.O., and W.B.; *Writing – Review and Editing*, J.M.d.J., P.W., M.O., and W.B.; *Visualization*, J.M.d.J. and W.B.; *Supervision*, W.B.; *Financial Acquisition*, P.W. and W.B.

ORCID

Wia Baron  <https://orcid.org/0000-0002-6673-4766>

REFERENCES

- Adams, J. C., & Lawler, J. (2011). The thrombospondins. *Cold Spring Harbor Perspectives in Biology*, 3(10), a009712. <https://doi.org/10.1101/cshperspect.a009712>
- Agrawal, S. M., Lau, L., & Yong, V. W. (2008). MMPs in the central nervous system: Where the good guys go bad. *Seminars in Cell & Developmental Biology*, 19(1), 42–51. <https://doi.org/10.1016/j.semcdb.2007.06.003>
- Aho, S., & Uitto, J. (1998). Two-hybrid analysis reveals multiple direct interactions for thrombospondin 1. *Matrix Biology*, 17(6), 401–412. [https://doi.org/10.1016/S0945-053X\(98\)90100-7](https://doi.org/10.1016/S0945-053X(98)90100-7)
- Anthony, D. C., Ferguson, B., Matyzak, M. K., Miller, K. M., Esiri, M. M., & Perry, V. H. (1997). Differential matrix metalloproteinase expression in cases of multiple sclerosis and stroke. *Neuropathology and Applied Neurobiology*, 23(5), 406–415. <https://doi.org/10.1111/j.1365-2990.1997.tb01315.x>
- Anthony, D. C., Miller, K. M., Fearn, S., Townsend, M. J., Opendakker, G., Wells, G., ... Perry, V. H. (1998). Matrix metalloproteinase expression in an experimentally-induced DTH model of multiple sclerosis in the rat CNS. *Journal of Neuroimmunology*, 87(1–2), 62–72. [https://doi.org/10.1016/S0165-5728\(98\)00046-0](https://doi.org/10.1016/S0165-5728(98)00046-0)
- Arnett, H. A., Fancy, S. P., Alberta, J. A., Zhao, C., Plant, S. R., Kaing, S., ... Stiles, C. D. (2004). bHLH transcription factor Olig1 is required to repair demyelinated lesions in the CNS. *Science*, 306(5704), 2111–2115. <https://doi.org/10.1126/science.1103709>
- Asch, A. S., Leung, L. L., Shapiro, J., & Nachman, R. L. (1986). Human brain glial cells synthesize thrombospondin. *Proceedings of the National Academy of Sciences of the United States of America*, 83(9), 2904–2908. <https://doi.org/10.1073/pnas.83.9.2904>
- Asher, R. A., Morgenstern, D. A., Fidler, P. S., Adcock, K. H., Oohira, A., Braistead, J. E., ... Fawcett, J. W. (2000). Neurocan is upregulated in injured brain and in cytokine-treated astrocytes. *Journal of Neuroscience*, 20(7), 2427–2438. <https://doi.org/10.1523/JNEUROSCI.20-07-02427.2000>
- Asher, R. A., Morgenstern, D. A., Shearer, M. C., Adcock, K. H., Pesheva, P., & Fawcett, J. W. (2002). Versican is upregulated in CNS injury and is a product of oligodendrocyte lineage cells. *Journal of Neuroscience*, 22(6), 2225–2236. <https://doi.org/10.1523/JNEUROSCI.22-06-02225.2002>
- Austin, J. W., Kang, C. E., Baumann, M. D., DiDiodato, L., Satkunendrarajah, K., Wilson, J. R., ... Fehlings, M. G. (2012). The effects of intrathecal injection of a hyaluronan-based hydrogel on inflammation, scarring and neurobehavioural outcomes in a rat model of severe spinal cord injury associated with arachnoiditis. *Biomaterials*, 33(18), 4555–4564. <https://doi.org/10.1016/j.biomaterials.2012.03.022>
- Back, S. A., Tuohy, T. M. F., Chen, H., Wallingford, N., Craig, A., Struve, J., ... Sherman, L. S. (2005). Hyaluronan accumulates in demyelinated lesions and inhibits oligodendrocyte progenitor maturation. *Nature Medicine*, 11(9), 966–972. <https://doi.org/10.1038/nm1279>
- Baron, W., Bijlard, M., Nomden, A., de Jonge, J. C., Teunissen, C. E., & Hoekstra, D. (2014). Sulfatide-mediated control of extracellular matrix-dependent oligodendrocyte maturation. *Glia*, 62(6), 927–942. <https://doi.org/10.1002/glia.22650>
- Baron, W., Colognato, H., & ffrench-Constant, C. (2005). Integrin-growth factor interactions as regulators of oligodendroglial development and function. *Glia*, 49(4), 467–479. <https://doi.org/10.1002/glia.20132>
- Baron, W., Shattil, S. J., & ffrench-Constant, C. (2002). The oligodendrocyte precursor mitogen PDGF stimulates proliferation by activation of alpha(v)beta3 integrins. *EMBO Journal*, 21(8), 1957–1966. <https://doi.org/10.1093/emboj/21.8.1957>
- Bar-Or, A., Nuttall, R. K., Duddy, M., Alter, A., Kim, H. J., Ifergan, I., ... Yong, V. W. (2003). Analyses of all matrix metalloproteinase members in leukocytes emphasize monocytes as major inflammatory mediators in multiple sclerosis. *Brain*, 126(Pt 12), 2738–2749. <https://doi.org/10.1093/brain/awg285>
- Bartsch, S., Bartsch, U., Dorries, U., Faissner, A., Weller, A., Eklöf, P., & Schachner, M. (1992). Expression of tenascin in the developing and adult cerebellar cortex. *Journal of Neuroscience*, 12(3), 736–749. <https://doi.org/10.1523/JNEUROSCI.12-03-00736.1992>
- Bein, K., & Simons, M. (2000). Thrombospondin type 1 repeats interact with matrix metalloproteinase 2. Regulation of metalloproteinase activity. *The Journal of Biological Chemistry*, 275(41), 32167–32173. <https://doi.org/10.1074/jbc.M003834200>
- Benešová, Y., Vašků, A., Novotná, H., Litzman, J., Štourač, P., Beránek, M., ... Bednařík, J. (2009). Matrix metalloproteinase-9 and matrix metalloproteinase-2 as biomarkers of various courses in multiple sclerosis. *Multiple Sclerosis Journal*, 15(3), 316–322. <https://doi.org/10.1177/1352458508099482>
- Bever, C. T. Jr., & Garver, D. W. (1995). Increased cathepsin B activity in multiple sclerosis brain. *Journal of the Neurological Sciences*, 131(1), 71–73. [https://doi.org/10.1016/0022-510X\(95\)00039-5](https://doi.org/10.1016/0022-510X(95)00039-5)
- Bignami, A., Hosley, M., & Dahl, D. (1993). Hyaluronic acid and hyaluronic acid-binding proteins in brain extracellular matrix. *Anatomy and Embryology (Berlin)*, 188(5), 419–433. <https://doi.org/10.1007/BF00190136>
- Bjelobaba, I., Begovic-Kupresanin, V., Pekovic, S., & Lavrnja, I. (2018). Animal models of multiple sclerosis: Focus on experimental autoimmune encephalomyelitis. *Journal of Neuroscience Research*, 96(6), 1021–1042. <https://doi.org/10.1002/jnr.24224>
- Blakemore, W. F. (1976). Invasion of Schwann-cells into spinal-cord of rat following local injections of lysolecithin. *Neuropathology and Applied Neurobiology*, 2(1), 21–39. <https://doi.org/10.1111/j.1365-2990.1976.tb00559.x>
- Blaschuk, K. L., Frost, E. E., & ffrench-Constant, C. (2000). The regulation of proliferation and differentiation in oligodendrocyte progenitor cells by alphaV integrins. *Development*, 127(9), 1961–1969.
- Bonneh-Barkay, D., & Wiley, C. A. (2009). Brain extracellular matrix in neurodegeneration. *Brain Pathology*, 19(4), 573–585. <https://doi.org/10.1111/j.1750-3639.2008.00195.x>
- Bornstein, P., & Sage, E. H. (2002). Matricellular proteins: Extracellular modulators of cell function. *Current Opinion in Cell Biology*, 14(5), 608–616. [https://doi.org/10.1016/S0955-0674\(02\)00361-7](https://doi.org/10.1016/S0955-0674(02)00361-7)
- Buttery, P. C., & ffrench-Constant, C. (1999). Laminin-2/integrin interactions enhance myelin membrane formation by oligodendrocytes. *Molecular and Cellular Neurosciences*, 14(3), 199–212. <https://doi.org/10.1006/mcne.1999.0781>
- Cannella, B., & Raine, C. S. (1995). The adhesion molecule and cytokine profile of multiple sclerosis lesions. *Annals of Neurology*, 37(4), 424–435. <https://doi.org/10.1002/ana.410370404>

- Castellazzi, M., Ligi, D., Contaldi, E., Quartana, D., Fonderico, M., Borgatti, L., ... Pugliatti, M. (2018). Multiplex matrix metalloproteinases analysis in the cerebrospinal fluid reveals potential specific patterns in multiple sclerosis patients. *Frontiers in Neurology*, 9, 1080. <https://doi.org/10.3389/fneur.2018.01080>
- Chabas, D., Baranzini, S. E., Mitchell, D., Bernard, C. C., Rittling, S. R., Denhardt, D. T., ... Steinman, L. (2001). The influence of the proinflammatory cytokine, osteopontin, on autoimmune demyelinating disease. *Science*, 294(5547), 1731–1735. <https://doi.org/10.1126/science.1062960>
- Chandler, S., Coates, R., Gearing, A., Lury, J., Wells, G., & Bone, E. (1995). Matrix metalloproteinases degrade myelin basic protein. *Neuroscience Letters*, 201(3), 223–226. [https://doi.org/10.1016/0304-3940\(95\)12173-0](https://doi.org/10.1016/0304-3940(95)12173-0)
- Chandler, S., Cossins, J., Lury, J., & Wells, G. (1996). Macrophage metalloelastase degrades matrix and myelin proteins and processes a tumour necrosis factor-alpha fusion protein. *Biochemical and Biophysical Research Communications*, 228(2), 421–429. <https://doi.org/10.1006/bbrc.1996.1677>
- Chang, A., Tourtellotte, W. W., Rudick, R., & Trapp, B. D. (2002). Premyelinating oligodendrocytes in chronic lesions of multiple sclerosis. *New England Journal of Medicine*, 346(3), 165–173. <https://doi.org/10.1056/NEJMoa010994>
- Chiquet-Ehrismann, R. (1991). Anti-adhesive molecules of the extracellular matrix. *Current Opinion in Cell Biology*, 3(5), 800–804. [https://doi.org/10.1016/0955-0674\(91\)90053-2](https://doi.org/10.1016/0955-0674(91)90053-2)
- Chiquet-Ehrismann, R. (2004). Tenascins. *International Journal of Biochemistry & Cell Biology*, 36(6), 986–990. <https://doi.org/10.1016/j.biocel.2003.12.002>
- Christopherson, K. S., Ullian, E. M., Stokes, C. C. A., Mallowney, C. E., Hell, J. W., Agah, A., ... Barres, B. A. (2005). Thrombospondins are astrocyte-secreted proteins that promote CNS synaptogenesis. *Cell*, 120(3), 421–433. <https://doi.org/10.1016/j.cell.2004.12.020>
- Clements, J. M., Cossins, J. A., Wells, G. M., Corkill, D. J., Helfrich, K., Wood, L. M., ... Miller, K. M. (1997). Matrix metalloproteinase expression during experimental autoimmune encephalomyelitis and effects of a combined matrix metalloproteinase and tumour necrosis factor-alpha inhibitor. *Journal of Neuroimmunology*, 74(1–2), 85–94.
- Colognato, H., Baron, W., Avellana-Adalid, V., Relvas, J. B., Baron-Van Evercooren, A., Georges-Labouesse, E., & ffrench-Constant, C. (2002). CNS integrins switch growth factor signalling to promote target-dependent survival. *Nature Cell Biology*, 4(11), 833–841. <https://doi.org/10.1038/ncb865>
- Colognato, H., & Tzvetanova, I. D. (2011). Glia unglued: How signals from the extracellular matrix regulate the development of myelinating glia. *Developmental Neurobiology*, 71(11), 924–955. <https://doi.org/10.1002/dneu.20966>
- Colognato, H., & Yurchenco, P. D. (2000). Form and function: The laminin family of heterotrimers. *Developmental Dynamics*, 218(2), 213–234. [https://doi.org/10.1002/\(SICI\)1097-0177\(200006\)218:2<213::AID-DVDY1>3.0.CO;2-R](https://doi.org/10.1002/(SICI)1097-0177(200006)218:2<213::AID-DVDY1>3.0.CO;2-R)
- Compston, A., & Coles, A. (2008). Multiple sclerosis. *Lancet*, 372(9648), 1502–1517. [https://doi.org/10.1016/S0140-6736\(08\)61620-7](https://doi.org/10.1016/S0140-6736(08)61620-7)
- Correale, J., & Farez, M. F. (2015). The role of astrocytes in multiple sclerosis progression. *Frontiers in Neurology*, 6, 180. <https://doi.org/10.3389/fneur.2015.00180>
- Correale, J., & Gaitan, M. I. (2015). Multiple sclerosis and environmental factors: The role of vitamin D, parasites, and Epstein-Barr virus infection. *Acta Neurologica Scandinavica*, 132(199), 46–55. <https://doi.org/10.1111/ane.12431>
- Cossins, J. A., Clements, J. M., Ford, J., Miller, K. M., Pigott, R., Vos, W., ... De Groot, C. J. A. (1997). Enhanced expression of MMP-7 and MMP-9 in demyelinating multiple sclerosis lesions. *Acta Neuropathologica*, 94(6), 590–598. <https://doi.org/10.1007/s004010050754>
- Cragg, B. (1979). Brain extracellular space fixed for electron microscopy. *Neuroscience Letters*, 15(2–3), 301–306. [https://doi.org/10.1016/0304-3940\(79\)96130-5](https://doi.org/10.1016/0304-3940(79)96130-5)
- Cuzner, M. L., Gveric, D., Strand, C., Loughlin, A. J., Paemen, L., Opendakker, G., & Newcombe, J. (1996). The expression of tissue-type plasminogen activator, matrix metalloproteinases and endogenous inhibitors in the central nervous system in multiple sclerosis: Comparison of stages in lesion evolution. *Journal of Neuropathology and Experimental Neurology*, 55(12), 1194–1204. <https://doi.org/10.1097/00005072-199612000-00002>
- Czopka, T., von Holst, A., ffrench-Constant, C., & Faissner, A. (2010). Regulatory mechanisms that mediate tenascin C-dependent inhibition of oligodendrocyte precursor differentiation. *Journal of Neuroscience*, 30(37), 12310–12322. <https://doi.org/10.1523/JNEUROSCI.4957-09.2010>
- Czopka, T., Von Holst, A., Schmidt, G., ffrench-Constant, C., & Faissner, A. (2009). Tenascin C and tenascin R similarly prevent the formation of myelin membranes in a RhoA-dependent manner, but antagonistically regulate the expression of myelin basic protein via a separate pathway. *Glia*, 57(16), 1790–1801. <https://doi.org/10.1002/glia.20891>
- Dahl, D., Perides, G., & Bignami, A. (1989). Axonal regeneration in old multiple sclerosis plaques. Immunohistochemical study with monoclonal antibodies to phosphorylated and non-phosphorylated neurofilament proteins. *Acta Neuropathologica*, 79(2), 154–159. <https://doi.org/10.1007/BF00294373>
- Dasilva, A. G., & Yong, V. W. (2008). Expression and regulation of matrix metalloproteinase-12 in experimental autoimmune encephalomyelitis and by bone marrow derived macrophages in vitro. *Journal of Neuroimmunology*, 199(1–2), 24–34. <https://doi.org/10.1016/j.jneur.2008.04.034>
- de la Vega Gallardo, N., Dittmer, M., Dombrowski, Y., & Fitzgerald, D. C. (2018). Regenerating CNS myelin: Emerging roles of regulatory T cells and CCN proteins. *Neurochemistry International*, 130, 104349. <https://doi.org/10.1016/j.neuint.2018.11.024>
- D'Ercole, A. J., Ye, P., & O'Kusky, J. R. (2002). Mutant mouse models of insulin-like growth factor actions in the central nervous system. *Neuropeptides*, 36(2–3), 209–220. <https://doi.org/10.1054/npep.2002.0893>
- Diaz-Sanchez, M., Williams, K., DeLuca, G. C., & Esiri, M. M. (2006). Protein co-expression with axonal injury in multiple sclerosis plaques. *Acta Neuropathologica*, 111(4), 289–299. <https://doi.org/10.1007/s00401-006-0045-0>
- Dityatev, A., & Fellin, T. (2008). Extracellular matrix in plasticity and epileptogenesis. *Neuron Glia Biology*, 4(3), 235–247. <https://doi.org/10.1017/S1740925X09000118>
- Dombrowski, Y., O'Hagan, T., Dittmer, M., Penalva, R., Mayoral, S. R., Bankhead, P., ... Fitzgerald, D. C. (2017). Regulatory T cells promote myelin regeneration in the central nervous system. *Nature Neuroscience*, 20(5), 674–680. <https://doi.org/10.1038/nn.4528>
- Dubois-Dalcq, M., & Murray, K. (2000). Why are growth factors important in oligodendrocyte physiology? *Pathologie Biologie*, 48(1), 80–86.
- Ebert, S., Schoeberl, T., Walczak, Y., Stoecker, K., Stempf, T., Moehle, C., ... Langmann, T. (2008). Chondroitin sulfate disaccharide stimulates microglia to adopt a novel regulatory phenotype. *Journal of Leukocyte Biology*, 84(3), 736–740. <https://doi.org/10.1189/jlb.0208138>
- Ercan, E., Han, J. M., Di Nardo, A., Winden, K., Han, M.-J., Hoyo, L., ... Sahin, M. (2017). Neuronal CTGF/CCN2 negatively regulates myelination in a mouse model of tuberous sclerosis complex. *Journal of Experimental Medicine*, 214(3), 681–697. <https://doi.org/10.1084/jem.20160446>
- Erickson, H. P., & Inglesias, J. L. (1984). A six-armed oligomer isolated from cell surface fibronectin preparations. *Nature*, 311(5983), 267–269. <https://doi.org/10.1038/311267a0>

- Esiri, M. M., & Morris, C. S. (1991). Immunocytochemical study of macrophages and microglial cells and extracellular matrix components in human CNS disease. 2. Non-neoplastic diseases. *Journal of the Neurological Sciences*, 101(1), 59–72. [https://doi.org/10.1016/0022-510X\(91\)90018-3](https://doi.org/10.1016/0022-510X(91)90018-3)
- España, J., Vilardell, C., Calvo, J., Juan, M., Vives, J., Urbano-Marquez, A., ... Cid, M. C. (1999). Fibronectin upregulates gelatinase B (MMP-9) and induces coordinated expression of gelatinase A (MMP-2) and its activator MT1-MMP (MMP-14) by human T lymphocyte cell lines. A process repressed through RAS/MAP kinase signaling pathways. *Blood*, 94(8), 2754–2766.
- Espitia Pinzon, N., Sanz-Morello, B., Brevé, J. J. P., Bol, J. G. J. M., Drukarch, B., Bauer, J., ... van Dam, A.-M. (2017). Astrocyte-derived tissue Transglutaminase affects fibronectin deposition, but not aggregation, during cuprizone-induced demyelination. *Scientific Reports*, 7, 40995. <https://doi.org/10.1038/srep40995>
- Fainardi, E., Castellazzi, M., Bellini, T., Manfrinato, M. C., Baldi, E., Casetta, I., ... Dallochio, F. (2006). Cerebrospinal fluid and serum levels and intrathecal production of active matrix metalloproteinase-9 (MMP-9) as markers of disease activity in patients with multiple sclerosis. *Mult Scler*, 12(3), 294–301. <https://doi.org/10.1191/135248506ms1274oa>
- Felts, P. A., Baker, T. A., & Smith, K. J. (1997). Conduction in segmentally demyelinated mammalian central axons. *Journal of Neuroscience*, 17(19), 7267–7277. <https://doi.org/10.1523/JNEUROSCI.17-19-07267.1997>
- Ferent, J., Zimmer, C., Durbec, P., Ruat, M., & Traiffort, E. (2013). Sonic Hedgehog signaling is a positive oligodendrocyte regulator during demyelination. *Journal of Neuroscience*, 33(5), 1759–1772. <https://doi.org/10.1523/JNEUROSCI.3334-12.2013>
- Fosang, A. J., Neame, P. J., Last, K., Hardingham, T. E., Murphy, G., & Hamilton, J. A. (1992). The interglobular domain of cartilage aggrecan is cleaved by PUMP, gelatinases, and cathepsin B. *Journal of Biological Chemistry*, 267(27), 19470–19474.
- Fowlkes, J. L., Serra, D. M., Bunn, R. C., Thraillkill, K. M., Enghild, J. J., & Nagase, H. (2004). Regulation of insulin-like growth factor (IGF)-I action by matrix metalloproteinase-3 involves selective disruption of IGF-I/IGF-binding protein-3 complexes. *Endocrinology*, 145(2), 620–626. <https://doi.org/10.1210/en.2003-0636>
- Franklin, R. J., & ffrench-Constant, C. (2008). Remyelination in the CNS: From biology to therapy. *Nature Reviews Neuroscience*, 9(11), 839–855. <https://doi.org/10.1038/nrn2480>
- Franklin, R. J., Zhao, C., & Sim, F. J. (2002). Ageing and CNS remyelination. *NeuroReport*, 13(7), 923–928. <https://doi.org/10.1097/00001756-200205240-00001>
- Frischer, J. M., Weigand, S. D., Guo, Y., Kale, N., Parisi, J. E., Pirkko, I., ... Lucchinetti, C. F. (2015). Clinical and pathological insights into the dynamic nature of the white matter multiple sclerosis plaque. *Annals of Neurology*, 78(5), 710–721. <https://doi.org/10.1002/ana.24497>
- Frischknecht, R., & Seidenbecher, C. I. (2008). The crosstalk of hyaluronan-based extracellular matrix and synapses. *Neuron Glia Biology*, 4(3), 249–257. <https://doi.org/10.1017/S1740925X09990226>
- Frost, E. E., Buttery, P. C., Milner, R., & ffrench-Constant, C. (1999). Integrins mediate a neuronal survival signal for oligodendrocytes. *Current Biology*, 9(21), 1251–1254. [https://doi.org/10.1016/S0960-9822\(99\)80506-5](https://doi.org/10.1016/S0960-9822(99)80506-5)
- Frost, E., Kiernan, B. W., Faissner, A., & ffrench-Constant, C. (1996). Regulation of oligodendrocyte precursor migration by extracellular matrix: Evidence for substrate-specific inhibition of migration by tenascin-C. *Developmental Neuroscience*, 18(4), 266–273. <https://doi.org/10.1159/000111416>
- Fünfschilling, U., Supplie, L. M., Mahad, D., Boretius, S., Saab, A. S., Edgar, J., ... Nave, K.-A. (2012). Glycolytic oligodendrocytes maintain myelin and long-term axonal integrity. *Nature*, 485(7399), 517–521. <https://doi.org/10.1038/nature11007>
- Fuss, B., Wintergerst, E. S., Bartsch, U., & Schachner, M. (1993). Molecular characterization and in situ mRNA localization of the neural recognition molecule J1–160/180: A modular structure similar to tenascin. *Journal of Cell Biology*, 120(5), 1237–1249. <https://doi.org/10.1083/jcb.120.5.1237>
- Gaesser, J. M., & Fyffe-Maricich, S. L. (2016). Intracellular signaling pathway regulation of myelination and remyelination in the CNS. *Experimental Neurology*, 283(Pt B), 501–511. <https://doi.org/10.1016/j.expneurol.2016.03.008>
- Garcion, E., Faissner, A., & ffrench-Constant, C. (2001). Knockout mice reveal a contribution of the extracellular matrix molecule tenascin-C to neural precursor proliferation and migration. *Development*, 128(13), 2485–2496.
- Garwood, J., Garcion, E., Dobbertin, A., Heck, N., Calco, V., ffrench-Constant, C., & Faissner, A. (2004). The extracellular matrix glycoprotein Tenascin-C is expressed by oligodendrocyte precursor cells and required for the regulation of maturation rate, survival and responsiveness to platelet-derived growth factor. *European Journal of Neuroscience*, 20(10), 2524–2540. <https://doi.org/10.1111/j.1460-9568.2004.03727.x>
- Giachelli, C. M., & Steitz, S. (2000). Osteopontin: A versatile regulator of inflammation and biomineralization. *Matrix Biology*, 19(7), 615–622. [https://doi.org/10.1016/S0945-053X\(00\)00108-6](https://doi.org/10.1016/S0945-053X(00)00108-6)
- Gijbels, K., Galardy, R. E., & Steinman, L. (1994). Reversal of experimental autoimmune encephalomyelitis with a hydroxamate inhibitor of matrix metalloproteases. *Journal of Clinical Investigation*, 94(6), 2177–2182. <https://doi.org/10.1172/JCI117578>
- Gijbels, K., Proost, P., Masure, S., Carton, H., Billiau, A., & Opdenakker, G. (1993). Gelatinase B is present in the cerebrospinal fluid during experimental autoimmune encephalomyelitis and cleaves myelin basic protein. *Journal of Neuroscience Research*, 36(4), 432–440. <https://doi.org/10.1002/jnr.490360409>
- Goldschmidt, T., Antel, J., König, F. B., Bruck, W., & Kuhlmann, T. (2009). Remyelination capacity of the MS brain decreases with disease chronicity. *Neurology*, 72(22), 1914–1921. <https://doi.org/10.1212/WNL.0b013e3181a8260a>
- Goncalves DaSilva, A., Liaw, L., & Yong, V. W. (2010). Cleavage of osteopontin by matrix metalloproteinase-12 modulates experimental autoimmune encephalomyelitis disease in C57BL/6 mice. *American Journal of Pathology*, 177(3), 1448–1458. <https://doi.org/10.2353/ajpath.2010.091081>
- Gotz, M., Bolz, J., Joester, A., & Faissner, A. (1997). Tenascin-C synthesis and influence on axonal growth during rat cortical development. *European Journal of Neuroscience*, 9(3), 496–506. <https://doi.org/10.1111/j.1460-9568.1997.tb01627.x>
- Gronski, T. J., Martin, R. L., Kobayashi, D. K., Walsh, B. C., Holman, M. C., Huber, M., ... Shapiro, S. D. (1997). Hydrolysis of a broad spectrum of extracellular matrix proteins by human macrophage elastase. *Journal of Biological Chemistry*, 272(18), 12189–12194. <https://doi.org/10.1074/jbc.272.18.12189>
- Gutowski, N. J., Newcombe, J., & Cuzner, M. L. (1999). Tenascin-R and C in multiple sclerosis lesions: Relevance to extracellular matrix remodelling. *Neuropathology and Applied Neurobiology*, 25(3), 207–214. <https://doi.org/10.1046/j.1365-2990.1999.00176.x>
- Haist, V., Ulrich, R., Kalkuhl, A., Deschl, U., & Baumgartner, W. (2012). Distinct spatio-temporal extracellular matrix accumulation within demyelinated spinal cord lesions in Theiler's murine encephalomyelitis. *Brain Pathology*, 22(2), 188–204. <https://doi.org/10.1111/j.1750-3639.2011.00518.x>
- Hanafy, K. A., & Sloane, J. A. (2011). Regulation of remyelination in multiple sclerosis. *FEBS Letters*, 585(23), 3821–3828. <https://doi.org/10.1016/j.febslet.2011.03.048>
- Hansmann, F., Herder, V., Kalkuhl, A., Haist, V., Zhang, N., Schaudien, D., ... Ulrich, R. (2012). Matrix metalloproteinase-12 deficiency ameliorates the clinical course and demyelination in Theiler's murine encephalomyelitis. *Acta Neuropathologica*, 124(1), 127–142. <https://doi.org/10.1007/s00401-012-0942-3>

- Harroch, S., Furtado, G. C., Brueck, W., Rosenbluth, J., Lafaille, J., Chao, M., ... Schlessinger, J. (2002). A critical role for the protein tyrosine phosphatase receptor type Z in functional recovery from demyelinating lesions. *Nature Genetics*, 32(3), 411–414. <https://doi.org/10.1038/ng1004>
- Hendrickx, D. A. E., van Scheppingen, J., van der Poel, M., Bossers, K., Schuurman, K. G., van Eden, C. G., ... Huitinga, I. (2017). Gene expression profiling of multiple sclerosis pathology identifies early patterns of demyelination surrounding chronic active lesions. *Frontiers in Immunology*, 8, 1810. <https://doi.org/10.3389/fimmu.2017.01810>
- Hibbitts, N., Yoshino, J., Le, T. Q., & Armstrong, R. C. (2012). Astrogliosis during acute and chronic cuprizone demyelination and implications for remyelination. *ASN Neuro*, 4(6), 393–408. <https://doi.org/10.1042/AN20120062>
- Holley, J. E., Gveric, D., Newcombe, J., Cuzner, M. L., & Gutowski, N. J. (2003). Astrocyte characterization in the multiple sclerosis glial scar. *Neuropathology and Applied Neurobiology*, 29(5), 434–444. <https://doi.org/10.1046/j.1365-2990.2003.00491.x>
- Huntley, G. W. (2012). Synaptic circuit remodelling by matrix metalloproteinases in health and disease. *Nature Reviews Neuroscience*, 13(11), 743–757. <https://doi.org/10.1038/nrn3320>
- Hur, E. M., Youssef, S., Haws, M. E., Zhang, S. Y., Sobel, R. A., & Steinman, L. (2007). Osteopontin-induced relapse and progression of autoimmune brain disease through enhanced survival of activated T cells. *Nature Immunology*, 8(1), 74–83. <https://doi.org/10.1038/ni1415>
- Hynes, R. O., & Yamada, K. M. (1982). Fibronectins: Multifunctional modular glycoproteins. *Journal of Cell Biology*, 95(2 Pt 1), 369–377. <https://doi.org/10.1083/jcb.95.2.369>
- Imai, K., Shikata, H., & Okada, Y. (1995). Degradation of vitronectin by matrix metalloproteinases-1, -2, -3, -7 and -9. *FEBS Letters*, 369(2–3), 249–251. [https://doi.org/10.1016/0014-5793\(95\)00752-u](https://doi.org/10.1016/0014-5793(95)00752-u)
- Iruela-Arispe, M. L. (2008). Regulation of thrombospondin1 by extracellular proteases. *Current Drug Targets*, 9(10), 863–868. <https://doi.org/10.2174/138945008785909365>
- Irvine, K. A., & Blakemore, W. F. (2008). Remyelination protects axons from demyelination-associated axon degeneration. *Brain*, 131(Pt 6), 1464–1477. <https://doi.org/10.1093/brain/awn080>
- Jäkel, S., Agirre, E., Mendanha Falcão, A., van Bruggen, D., Lee, K. W., Knuesel, I., ... Castelo-Branco, G. (2019). Altered human oligodendrocyte heterogeneity in multiple sclerosis. *Nature*, 566(7745), 543–547. <https://doi.org/10.1038/s41586-019-0903-2>
- Javaid, M. A., Abdallah, M. N., Ahmed, A. S., & Sheikh, Z. (2013). Matrix metalloproteinases and their pathological upregulation in multiple sclerosis: An overview. *Acta Neurologica Belgica*, 113(4), 381–390. <https://doi.org/10.1007/s13760-013-0239-x>
- Jeffery, N. D., & Blakemore, W. F. (1995). Remyelination of mouse spinal cord axons demyelinated by local injection of lysolecithin. *Journal of Neurocytology*, 24(10), 775–781. <https://doi.org/10.1007/bf01191213>
- Jeffery, N. D., & Blakemore, W. F. (1997). Locomotor deficits induced by experimental spinal cord demyelination are abolished by spontaneous remyelination. *Brain*, 120(Pt 1), 27–37. <https://doi.org/10.1093/brain/120.1.27>
- John, A. S., Hu, X., Rothman, V. L., & Tuszyński, G. P. (2009). Thrombospondin-1 (TSP-1) up-regulates tissue inhibitor of metalloproteinase-1 (TIMP-1) production in human tumor cells: Exploring the functional significance in tumor cell invasion. *Experimental and Molecular Pathology*, 87(3), 184–188. <https://doi.org/10.1016/j.yexmp.2009.09.002>
- John, G. R., Chen, L., Rivieccio, M. A., Melendez-Vasquez, C. V., Hartley, A., & Brosnan, C. F. (2004). Interleukin-1 β induces a reactive astroglial phenotype via deactivation of the Rho GTPase-Rock axis. *Journal of Neuroscience*, 24(11), 2837–2845. <https://doi.org/10.1523/JNEUROSCI.4789-03.2004>
- John, G. R., Lee, S. C., & Brosnan, C. F. (2003). Cytokines: Powerful regulators of glial cell activation. *Neuroscientist*, 9(1), 10–22. <https://doi.org/10.1177/1073858402239587>
- John, G. R., Lee, S. C., Song, X., Rivieccio, M., & Brosnan, C. F. (2005). IL-1-regulated responses in astrocytes: Relevance to injury and recovery. *Glia*, 49(2), 161–176. <https://doi.org/10.1002/glia.20109>
- John, G. R., Shankar, S. L., Shafit-Zagardo, B., Massimi, A., Lee, S. C., Raine, C. S., & Brosnan, C. F. (2002). Multiple sclerosis: Re-expression of a developmental pathway that restricts oligodendrocyte maturation. *Nature Medicine*, 8(10), 1115–1121. <https://doi.org/10.1038/nm781>
- Jones, E. V., & Bouvier, D. S. (2014). Astrocyte-secreted matricellular proteins in CNS remodelling during development and disease. *Neural Plasticity*, 2014, 321209. <https://doi.org/10.1155/2014/321209>
- Karus, M., Ulc, A., Ehrlich, M., Czopka, T., Hennen, E., Fischer, J., ... Faissner, A. (2016). Regulation of oligodendrocyte precursor maintenance by chondroitin sulphate glycosaminoglycans. *Glia*, 64(2), 270–286. <https://doi.org/10.1002/glia.22928>
- Keough, M. B., Rogers, J. A., Zhang, P., Jensen, S. K., Stephenson, E. L., Chen, T., ... Yong, V. W. (2016). An inhibitor of chondroitin sulfate proteoglycan synthesis promotes central nervous system remyelination. *Nature Communications*, 7, 11312. <https://doi.org/10.1038/ncomms11312>
- Kiernan, B. W., Gotz, B., Faissner, A., & French-Constant, C. (1996). Tenascin-C inhibits oligodendrocyte precursor cell migration by both adhesion-dependent and adhesion-independent mechanisms. *Molecular and Cellular Neurosciences*, 7(4), 322–335. <https://doi.org/10.1006/mcne.1996.0024>
- Kieseier, B. C., Kiefer, R., Clements, J. M., Miller, K., Wells, G. M., Schweitzer, T., ... Hartung, H. P. (1998). Matrix metalloproteinase-9 and -7 are regulated in experimental autoimmune encephalomyelitis. *Brain*, 121(Pt 1), 159–166. <https://doi.org/10.1093/brain/121.1.159>
- Kieseier, B. C., Seifert, T., Giovannoni, G., & Hartung, H. P. (1999). Matrix metalloproteinases in inflammatory demyelination: Targets for treatment. *Neurology*, 53(1), 20–25. <https://doi.org/10.1212/wnl.53.1.20>
- Kondo, A., Nakano, T., & Suzuki, K. (1987). Blood-brain barrier permeability to horseradish peroxidase in twitcher and cuprizone-intoxicated mice. *Brain Research*, 425(1), 186–190. [https://doi.org/10.1016/0006-8993\(87\)90499-9](https://doi.org/10.1016/0006-8993(87)90499-9)
- Koning, N., Bo, L., Hoek, R. M., & Huitinga, I. (2007). Downregulation of macrophage inhibitory molecules in multiple sclerosis lesions. *Annals of Neurology*, 62(5), 504–514. <https://doi.org/10.1002/ana.21220>
- Kornek, B., Storch, M. K., Weissert, R., Wallstroem, E., Steffler, A., Olsson, T., ... Lassmann, H. (2000). Multiple sclerosis and chronic autoimmune encephalomyelitis: A comparative quantitative study of axonal injury in active, inactive, and remyelinated lesions. *American Journal of Pathology*, 157(1), 267–276. [https://doi.org/10.1016/S0002-9440\(10\)64537-3](https://doi.org/10.1016/S0002-9440(10)64537-3)
- Kotter, M. R., Li, W. W., Zhao, C., & Franklin, R. J. (2006). Myelin impairs CNS remyelination by inhibiting oligodendrocyte precursor cell differentiation. *Journal of Neuroscience*, 26(1), 328–332. <https://doi.org/10.1523/JNEUROSCI.2615-05.2006>
- Kuhlmann, T., Ludwin, S., Prat, A., Antel, J., Bruck, W., & Lassmann, H. (2017). An updated histological classification system for multiple sclerosis lesions. *Acta Neuropathologica*, 133(1), 13–24. <https://doi.org/10.1007/s00401-016-1653-y>
- Kuhlmann, T., Miron, V., Cui, Q., Wegner, C., Antel, J., & Bruck, W. (2008). Differentiation block of oligodendroglial progenitor cells as a cause for remyelination failure in chronic multiple sclerosis. *Brain*, 131(Pt 7), 1749–1758. <https://doi.org/10.1093/brain/awn096>
- Kwok, J. C., Dick, G., Wang, D., & Fawcett, J. W. (2011). Extracellular matrix and perineuronal nets in CNS repair. *Developmental Neurobiology*, 71(11), 1073–1089. <https://doi.org/10.1002/dneu.20974>
- Lafrenaye, A. D., & Fuss, B. (2010). Focal adhesion kinase can play unique and opposing roles in regulating the morphology of differentiating oligodendrocytes. *Journal of Neurochemistry*, 115(1), 269–282. <https://doi.org/10.1111/j.1471-4159.2010.06926.x>

- Lamond, R., & Barnett, S. C. (2013). Schwann cells but not olfactory ensheathing cells inhibit CNS myelination via the secretion of connective tissue growth factor. *Journal of Neuroscience*, 33(47), 18686–18697. <https://doi.org/10.1523/JNEUROSCI.3233-13.2013>
- Lamprianou, S., Chatzopoulou, E., Thomas, J. L., Bouyain, S., & Harroch, S. (2011). A complex between contactin-1 and the protein tyrosine phosphatase PTPRZ controls the development of oligodendrocyte precursor cells. *Proceedings of the National Academy of Sciences of the United States of America*, 108(42), 17498–17503. <https://doi.org/10.1073/pnas.1108774108>
- Larsen, P. H., DaSilva, A. G., Conant, K., & Yong, V. W. (2006). Myelin formation during development of the CNS is delayed in matrix metalloproteinase-9 and -12 null mice. *Journal of Neuroscience*, 26(8), 2207–2214. <https://doi.org/10.1523/JNEUROSCI.1880-05.2006>
- Larsen, P. H., Wells, J. E., Stallcup, W. B., Opdenakker, G., & Yong, V. W. (2003). Matrix metalloproteinase-9 facilitates remyelination in part by processing the inhibitory NG2 proteoglycan. *Journal of Neuroscience*, 23(35), 11127–11135. <https://doi.org/10.1523/JNEUROSCI.23-35-11127.2003>
- Larsen, P. H., & Yong, V. W. (2004). The expression of matrix metalloproteinase-12 by oligodendrocytes regulates their maturation and morphological differentiation. *Journal of Neuroscience*, 24(35), 7597–7603. <https://doi.org/10.1523/JNEUROSCI.2092-04.2004>
- Lau, L. W., Cua, R., Keough, M. B., Haylock-Jacobs, S., & Yong, V. W. (2013). Pathophysiology of the brain extracellular matrix: A new target for remyelination. *Nature Reviews Neuroscience*, 14(10), 722–729. <https://doi.org/10.1038/nrn3550>
- Lau, L. W., Keough, M. B., Haylock-Jacobs, S., Cua, R., Döring, A., Sloka, S., ... Yong, V. W. (2012). Chondroitin sulfate proteoglycans in demyelinated lesions impair remyelination. *Annals of Neurology*, 72(3), 419–432. <https://doi.org/10.1002/ana.23599>
- Lee, Y., Morrison, B. M., Li, Y., Lengacher, S., Farah, M. H., Hoffman, P. N., ... Rothstein, J. D. (2012). Oligodendroglia metabolically support axons and contribute to neurodegeneration. *Nature*, 487(7408), 443–448. <https://doi.org/10.1038/nature11314>
- Leiton, C. V., Aranmolate, A., Eyermann, C., Menezes, M. J., Escobar-Hoyos, L. F., Husain, S., ... Colognato, H. (2015). Laminin promotes metalloproteinase-mediated dystroglycan processing to regulate oligodendrocyte progenitor cell proliferation. *Journal of Neurochemistry*, 135(3), 522–538. <https://doi.org/10.1111/jnc.13241>
- Leppert, D., Lindberg, R. L., Kappos, L., & Leib, S. L. (2001). Matrix metalloproteinases: Multifunctional effectors of inflammation in multiple sclerosis and bacterial meningitis. *Brain Research Reviews*, 36(2–3), 249–257. [https://doi.org/10.1016/S0165-0173\(01\)00101-1](https://doi.org/10.1016/S0165-0173(01)00101-1)
- Levine, J. M., & Reynolds, R. (1999). Activation and proliferation of endogenous oligodendrocyte precursor cells during ethidium bromide-induced demyelination. *Experimental Neurology*, 160(2), 333–347. <https://doi.org/10.1006/exnr.1999.7224>
- Liedtke, W., Cannella, B., Mazzaccaro, R. J., Clements, J. M., Miller, K. M., Wucherpfenning, K. W., ... Raine, C. S. (1998). Effective treatment of models of multiple sclerosis by matrix metalloproteinase inhibitors. *Annals of Neurology*, 44(1), 35–46. <https://doi.org/10.1002/ana.410440110>
- Lindberg, R. L., De Groot, C. J., Montagne, L., Freitag, P., van der Valk, P., Kappos, L., & Leppert, D. (2001). The expression profile of matrix metalloproteinases (MMPs) and their inhibitors (TIMPs) in lesions and normal appearing white matter of multiple sclerosis. *Brain*, 124(Pt 9), 1743–1753. <https://doi.org/10.1093/brain/124.9.1743>
- Lloyd, A. F., & Miron, V. E. (2019). The pro-remyelination properties of microglia in the central nervous system. *Nature Reviews Neuroscience*, 15(8), 447–458. <https://doi.org/10.1038/s41582-019-0184-2>
- Lu, P., Takai, K., Weaver, V. M., & Werb, Z. (2011). Extracellular matrix degradation and remodeling in development and disease. *Cold Spring Harbor Perspectives in Biology*, 3(12), a005058. <https://doi.org/10.1101/cshperspect.a005058>
- Lublin, F. D., & Reingold, S. C. (1996). Defining the clinical course of multiple sclerosis: Results of an international survey. national multiple sclerosis society (USA) advisory committee on clinical trials of new agents in multiple sclerosis. *Neurology*, 46(4), 907–911. <https://doi.org/10.1212/wnl.46.4.907>
- Lucchinetti, C., Bruck, W., Parisi, J., Scheithauer, B., Rodriguez, M., & Lassmann, H. (1999). A quantitative analysis of oligodendrocytes in multiple sclerosis lesions. A study of 113 cases. *Brain*, 122 (Pt. 12), 2279–2295. <https://doi.org/10.1093/brain/122.12.2279>
- Luchetti, S., Fransen, N. L., van Eden, C. G., Ramaglia, V., Mason, M., & Huitinga, I. (2018). Progressive multiple sclerosis patients show substantial lesion activity that correlates with clinical disease severity and sex: A retrospective autopsy cohort analysis. *Acta Neuropathologica*, 135(4), 511–528. <https://doi.org/10.1007/s00401-018-1818-y>
- Maeda, A., & Sobel, R. A. (1996). Matrix metalloproteinases in the normal human central nervous system, microglial nodules, and multiple sclerosis lesions. *Journal of Neuropathology and Experimental Neurology*, 55(3), 300–309. <https://doi.org/10.1097/00005072-199603000-00005>
- Mai, J., Sameni, M., Mikkelsen, T., & Sloane, B. F. (2002). Degradation of extracellular matrix protein tenascin-C by cathepsin B: An interaction involved in the progression of gliomas. *Biological Chemistry*, 383(9), 1407–1413. <https://doi.org/10.1515/BC.2002.159>
- Maier, O., van der Heide, T., van Dam, A. M., Baron, W., de Vries, H., & Hoekstra, D. (2005). Alteration of the extracellular matrix interferes with raft association of neurofascin in oligodendrocytes. Potential significance for multiple sclerosis? *Molecular and Cellular Neurosciences*, 28(2), 390–401. <https://doi.org/10.1016/j.mcn.2004.09.012>
- Mallucci, G., Peruzzotti-Jametti, L., Bernstock, J. D., & Pluchino, S. (2015). The role of immune cells, glia and neurons in white and gray matter pathology in multiple sclerosis. *Progress in Neurobiology*, 127–128, 1–22. <https://doi.org/10.1016/j.pneurobio.2015.02.003>
- Manicone, A. M., Birkland, T. P., Lin, M., Betsuyaku, T., van Rooijen, N., Lohi, J., ... Parks, W. C. (2009). Epilysin (MMP-28) restrains early macrophage recruitment in *Pseudomonas aeruginosa* pneumonia. *Journal of Immunology*, 182(6), 3866–3876. <https://doi.org/10.4049/jimmunol.0713949>
- McCawley, L. J., & Matrisian, L. M. (2001). Matrix metalloproteinases: They're not just for matrix anymore!. *Current Opinion in Cell Biology*, 13(5), 534–540. [https://doi.org/10.1016/S0955-0674\(00\)00248-9](https://doi.org/10.1016/S0955-0674(00)00248-9)
- McMahon, E. J., Suzuki, K., & Matsushima, G. K. (2002). Peripheral macrophage recruitment in cuprizone-induced CNS demyelination despite an intact blood-brain barrier. *Journal of Neuroimmunology*, 130(1–2), 32–45. [https://doi.org/10.1016/S0165-5728\(02\)00205-9](https://doi.org/10.1016/S0165-5728(02)00205-9)
- Menn, B., Garcia-Verdugo, J. M., Yaschine, C., Gonzalez-Perez, O., Rowitch, D., & Alvarez-Buylla, A. (2006). Origin of oligodendrocytes in the subventricular zone of the adult brain. *Journal of Neuroscience*, 26(30), 7907–7918. <https://doi.org/10.1523/JNEUROSCI.1299-06.2006>
- Midwood, K. S., Chiquet, M., Tucker, R. P., & Orend, G. (2016). Tenascin-C at a glance. *Journal of Cell Science*, 129(23), 4321–4327. <https://doi.org/10.1242/jcs.190546>
- Milner, R., Crocker, S. J., Hung, S., Wang, X., Frausto, R. F., & del Zoppo, G. J. (2007). Fibronectin- and vitronectin-induced microglial activation and matrix metalloproteinase-9 expression is mediated by integrins $\alpha 5 \beta 1$ and $\alpha 4 \beta 1$. *Journal of Immunology*, 178(12), 8158–8167. <https://doi.org/10.4049/jimmunol.178.12.8158>
- Milner, R., Edwards, G., Streuli, C., & ffrench-Constant, C. (1996). A role in migration for the $\alpha V \beta 1$ integrin expressed on oligodendrocyte precursors. *Journal of Neuroscience*, 16(22), 7240–7252.
- Miron, V. E. (2017). Microglia-driven regulation of oligodendrocyte lineage cells, myelination, and remyelination. *Journal of Leukocyte Biology*, 101(5), 1103–1108. <https://doi.org/10.1189/jlb.3RI1116-494R>

- Miron, V. E., Boyd, A., Zhao, J.-W., Yuen, T. J., Ruckh, J. M., Shadrach, J. L., ... ffrench-Constant, C. (2013). M2 microglia and macrophages drive oligodendrocyte differentiation during CNS remyelination. *Nature Neuroscience*, 16(9), 1211–1218. <https://doi.org/10.1038/nn.3469>
- Mohan, H., Krumbholz, M., Sharma, R., Eisele, S., Junker, A., Sixt, M., ... Meinel, E. (2010). Extracellular matrix in multiple sclerosis lesions: Fibrillar collagens, biglycan and decorin are upregulated and associated with infiltrating immune cells. *Brain Pathology*, 20(5), 966–975. <https://doi.org/10.1111/j.1750-3639.2010.00399.x>
- Moyon, S., Dubessy, A. L., Aigrot, M. S., Trotter, M., Huang, J. K., Dauphinot, L., ... Lubetzki, C. (2015). Demyelination causes adult CNS progenitors to revert to an immature state and express immune cues that support their migration. *Journal of Neuroscience*, 35(1), 4–20. <https://doi.org/10.1523/JNEUROSCI.0849-14.2015>
- Muir, E. M., Adcock, K. H., Morgenstern, D. A., Clayton, R., von Stillfried, N., Rhodes, K., ... Rogers, J. H. (2002). Matrix metalloproteinases and their inhibitors are produced by overlapping populations of activated astrocytes. *Molecular Brain Research*, 100(1–2), 103–117. [https://doi.org/10.1016/S0169-328X\(02\)00132-8](https://doi.org/10.1016/S0169-328X(02)00132-8)
- Muramatsu, R., Kuroda, M., Matoba, K., Lin, H., Takahashi, C., Koyama, Y., & Yamashita, T. (2015). Prostacyclin prevents pericyte loss and demyelination induced by lysophosphatidylcholine in the central nervous system. *Journal of Biological Chemistry*, 290(18), 11515–11525. <https://doi.org/10.1074/jbc.M114.587253>
- Murphy, G., Cockett, M. I., Ward, R. V., & Docherty, A. J. (1991). Matrix metalloproteinase degradation of elastin, type IV collagen and proteoglycan. A quantitative comparison of the activities of 95 kDa and 72 kDa gelatinases, stromelysins-1 and -2 and punctuated metalloproteinase (PUMP). *Biochemical Journal*, 277(1), 277–279. <https://doi.org/10.1042/bj2770277>
- Nagy, N., Kuipers, H. F., Marshall, P. L., Wang, E., Kaber, G., & Bollyky, P. L. (2019). Hyaluronan in immune dysregulation and autoimmune diseases. *Matrix Biology*, 78–79, 292–313. <https://doi.org/10.1016/j.matbio.2018.03.022>
- Nair, A., Frederick, T. J., & Miller, S. D. (2008). Astrocytes in multiple sclerosis: A product of their environment. *Cellular and Molecular Life Sciences*, 65(17), 2702–2720. <https://doi.org/10.1007/s00018-008-8059-5>
- Nicholson, C., & Sykova, E. (1998). Extracellular space structure revealed by diffusion analysis. *Trends in Neurosciences*, 21(5), 207–215. [https://doi.org/10.1016/S0166-2236\(98\)01261-2](https://doi.org/10.1016/S0166-2236(98)01261-2)
- Norenberg, U., Hubert, M., & Rathjen, F. G. (1996). Structural and functional characterization of tenascin-R (restrictin), an extracellular matrix glycoprotein of glial cells and neurons. *International Journal of Developmental Neuroscience*, 14(3), 217–231. [https://doi.org/10.1016/0736-5748\(96\)00009-3](https://doi.org/10.1016/0736-5748(96)00009-3)
- Oh, L. Y., Larsen, P. H., Krekoski, C. A., Edwards, D. R., Donovan, F., Werb, Z., & Yong, V. W. (1999). Matrix metalloproteinase-9/gelatinase B is required for process outgrowth by oligodendrocytes. *Journal of Neuroscience*, 19(19), 8464–8475. <https://doi.org/10.1523/JNEUROSCI.19-19-08464.1999>
- Olsson, T., Barcellos, L. F., & Alfredsson, L. (2017). Interactions between genetic, lifestyle and environmental risk factors for multiple sclerosis. *Nature Reviews Neurology*, 13(1), 25–36. <https://doi.org/10.1038/nrn.2016.187>
- Ohashi, T., Edamatsu, M., Bekku, Y., & Carulli, D. (2015). The hyaluronan and proteoglycan link proteins: Organizers of the brain extracellular matrix and key molecules for neuronal function and plasticity. *Experimental Neurology*, 274(Pt B), 134–144. <https://doi.org/10.1016/j.expneurol.2015.09.010>
- Owens, M. R., & Cimino, C. D. (1982). Synthesis of fibronectin by the isolated perfused rat liver. *Blood*, 59(6), 1305–1309. <https://doi.org/10.1182/blood.V59.6.1305.1305>
- Page-McCaw, A., Ewald, A. J., & Werb, Z. (2007). Matrix metalloproteinases and the regulation of tissue remodelling. *Nature Reviews Molecular Cell Biology*, 8(3), 221–233. <https://doi.org/10.1038/nrm2125>
- Pankov, R., & Yamada, K. M. (2002). Fibronectin at a glance. *Journal of Cell Science*, 115(Pt 20), 3861–3863. <https://doi.org/10.1242/jcs.00059>
- Papadopoulos, D., Pham-Dinh, D., & Reynolds, R. (2006). Axon loss is responsible for chronic neurological deficit following inflammatory demyelination in the rat. *Experimental Neurology*, 197(2), 373–385. <https://doi.org/10.1016/j.expneurol.2005.10.033>
- Park, C., Ponath, G., Levine-Ritterman, M., Bull, E., Swanson, E. C., De Jager, P. L., ... Pitt, D. (2019). The landscape of myeloid and astrocyte phenotypes in acute multiple sclerosis lesions. *Acta Neuropathologica Commun*, 7(1), 130. <https://doi.org/10.1186/s40478-019-0779-2>
- Patani, R., Balaratnam, M., Vora, A., & Reynolds, R. (2007). Remyelination can be extensive in multiple sclerosis despite a long disease course. *Neuropathology and Applied Neurobiology*, 33(3), 277–287. <https://doi.org/10.1111/j.1365-2990.2007.00805.x>
- Patrikios, P., Stadelmann, C., Kutzelnigg, A., Rauschka, H., Schmidbauer, M., Laursen, H., ... Lassmann, H. (2006). Remyelination is extensive in a subset of multiple sclerosis patients. *Brain*, 129(Pt 12), 3165–3172. <https://doi.org/10.1093/brain/awl217>
- Peferoen, L. A. N., Vogel, D. Y. S., Ummenthum, K., Breur, M., Heijnen, P. D. A. M., Gerritsen, W. H., ... Amor, S. (2015). Activation status of human microglia is dependent on lesion formation stage and remyelination in multiple sclerosis. *Journal of Neuropathology and Experimental Neurology*, 74(1), 48–63. <https://doi.org/10.1097/NEN.0000000000000149>
- Pendleton, J. C., Shablott, M. J., Gary, D. S., Belegu, V., Hurtado, A., Malone, M. L., & McDonald, J. W. (2013). Chondroitin sulfate proteoglycans inhibit oligodendrocyte myelination through PTPsigma. *Experimental Neurology*, 247, 113–121. <https://doi.org/10.1016/j.expneurol.2013.04.003>
- Pesheva, P., Gloor, S., Schachner, M., & Probstmeier, R. (1997). Tenascin-R is an intrinsic autocrine factor for oligodendrocyte differentiation and promotes cell adhesion by a sulfatide-mediated mechanism. *Journal of Neuroscience*, 17(12), 4642–4651. <https://doi.org/10.1523/JNEUROSCI.17-12-04642.1997>
- Pesheva, P., Spiess, E., & Schachner, M. (1989). J1-160 and J1-180 are oligodendrocyte-secreted nonpermissive substrates for cell adhesion. *Journal of Cell Biology*, 109(4 Pt 1), 1765–1778. <https://doi.org/10.1083/jcb.109.4.1765>
- Praet, J., Guglielmetti, C., Berneman, Z., Van der Linden, A., & Ponsaerts, P. (2014). Cellular and molecular neuropathology of the cuprizone mouse model: Clinical relevance for multiple sclerosis. *Neuroscience and Biobehavioral Reviews*, 47, 485–505. <https://doi.org/10.1016/j.neubiorev.2014.10.004>
- Preston, M., Gong, X. I., Su, W., Matsumoto, S. G., Banine, F., Winkler, C., ... Sherman, L. S. (2013). Digestion products of the PH20 hyaluronidase inhibit remyelination. *Annals of Neurology*, 73(2), 266–280. <https://doi.org/10.1002/ana.23788>
- Prieto, A. L., Jones, F. S., Cunningham, B. A., Crossin, K. L., & Edelman, G. M. (1990). Localization during development of alternatively spliced forms of cytotactin mRNA by in situ hybridization. *Journal of Cell Biology*, 111(2), 685–698. <https://doi.org/10.1083/jcb.111.2.685>
- Prineas, J. W., Kwon, E. E., Goldenberg, P. Z., Ilyas, A. A., Quarles, R. H., Benjamins, J. A., & Sprinkle, T. J. (1989). Multiple sclerosis. Oligodendrocyte proliferation and differentiation in fresh lesions. *Laboratory Investigation*, 61(5), 489–503.
- Proost, P., Van Damme, J., & Opdenakker, G. (1993). Leukocyte gelatinase B cleavage releases encephalitogens from human myelin basic protein. *Biochemical and Biophysical Research Communications*, 192(3), 1175–1181. <https://doi.org/10.1006/bbrc.1993.1540>
- Pu, A., Stephenson, E. L., & Yong, V. W. (2018). The extracellular matrix: Focus on oligodendrocyte biology and targeting CSPGs for remyelination therapies. *Glia*, 66(9), 1809–1825. <https://doi.org/10.1002/glia.23333>

- Qin, J., Sikkema, A. H., van der Bij, K., de Jonge, J. C., Klappe, K., Nies, V., ... Baron, W. (2017). GD1a overcomes inhibition of myelination by fibronectin via activation of protein kinase A: Implications for multiple sclerosis. *Journal of Neuroscience*, 37(41), 9925–9938. <https://doi.org/10.1523/JNEUROSCI.0103-17.2017>
- Rahimi, Z., Abdan, Z., Rahimi, Z., Razazian, N., Shiri, H., Vaisi-Raygani, A., ... Moradi, M.-T. (2016). Functional promoter polymorphisms of MMP-2 C-735T and MMP-9 C-1562T and their synergism with MMP-7 A-181G in multiple sclerosis. *Immunological Investigations*, 45(6), 543–552. <https://doi.org/10.1080/08820139.2016.1180303>
- Raine, C. S., & Wu, E. (1993). Multiple sclerosis: Remyelination in acute lesions. *Journal of Neuropathology and Experimental Neurology*, 52(3), 199–204. <https://doi.org/10.1097/00005072-199305000-00003>
- Rauch, U. (2007). Brain matrix: Structure, turnover and necessity. *Biochemical Society Transactions*, 35(Pt 4), 656–660. <https://doi.org/10.1042/BST0350656>
- Relucio, J., Tzvetanova, I. D., Ao, W., Lindquist, S., & Colognato, H. (2009). Laminin alters fyn regulatory mechanisms and promotes oligodendrocyte development. *Journal of Neuroscience*, 29(38), 11794–11806. <https://doi.org/10.1523/JNEUROSCI.0888-09.2009>
- Relvas, J. B., Setzu, A., Baron, W., Buttery, P. C., LaFlamme, S. E., Franklin, R. J., & ffrench-Constant, C. (2001). Expression of dominant-negative and chimeric subunits reveals an essential role for beta1 integrin during myelination. *Current Biology*, 11(13), 1039–1043. [https://doi.org/10.1016/s0960-9822\(01\)00292-5](https://doi.org/10.1016/s0960-9822(01)00292-5)
- Reynolds, R., Dawson, M., Papadopoulos, D., Polito, A., Di Bello, I. C., Pham-Dinh, D., & Levine, J. (2002). The response of NG2-expressing oligodendrocyte progenitors to demyelination in MOG-EAE and MS. *Journal of Neurocytology*, 31(6–7), 523–536.
- Risher, W. C., & Eroglu, C. (2012). Thrombospondins as key regulators of synaptogenesis in the central nervous system. *Matrix Biology*, 31(3), 170–177. <https://doi.org/10.1016/j.matbio.2012.01.004>
- Roch, L., Hecker, M., Friess, J., Angerer, I. C., Koczan, D., Fitzner, B., ... Zettl, U. K. (2017). High-resolution expression profiling of peripheral blood CD8(+) cells in patients with multiple sclerosis displays fingolimod-induced immune cell redistribution. *Molecular Neurobiology*, 54(7), 5511–5525. <https://doi.org/10.1007/s12035-016-0075-0>
- Rodriguez-Manzanique, J. C., Lane, T. F., Ortega, M. A., Hynes, R. O., Lawler, J., & Iruela-Arispe, M. L. (2001). Thrombospondin-1 suppresses spontaneous tumor growth and inhibits activation of matrix metalloproteinase-9 and mobilization of vascular endothelial growth factor. *Proceedings of the National Academy of Sciences of the United States of America*, 98(22), 12485–12490. <https://doi.org/10.1073/pnas.171460498>
- Rolls, A., Shechter, R., London, A., Segev, Y., Jacob-Hirsch, J., Amariglio, N., ... Schwartz, M. (2008). Two faces of chondroitin sulfate proteoglycan in spinal cord repair: A role in microglia/macrophage activation. *PLoS Medicine*, 5(8), e171. <https://doi.org/10.1371/journal.pmed.0050171>
- Rosati, G. (2001). The prevalence of multiple sclerosis in the world: An update. *Neurological Sciences*, 22(2), 117–139. <https://doi.org/10.1007/s100720170011>
- Rosenberg, G. A. (2002). Matrix metalloproteinases and neuroinflammation in multiple sclerosis. *Neuroscientist*, 8(6), 586–595. <https://doi.org/10.1177/1073858402238517>
- Rosenberg, G. A., Kornfeld, M., Estrada, E., Kelley, R. O., Liotta, L. A., & Stetler-Stevenson, W. G. (1992). TIMP-2 reduces proteolytic opening of blood-brain barrier by type IV collagenase. *Brain Research*, 576(2), 203–207. [https://doi.org/10.1016/0006-8993\(92\)90681-x](https://doi.org/10.1016/0006-8993(92)90681-x)
- Rozario, T., & DeSimone, D. W. (2010). The extracellular matrix in development and morphogenesis: A dynamic view. *Developmental Biology*, 341(1), 126–140. <https://doi.org/10.1016/j.ydbio.2009.10.026>
- Ruoslahti, E. (1996). Brain extracellular matrix. *Glycobiology*, 6(5), 489–492. <https://doi.org/10.1093/glycob/6.5.489>
- Sajad, M., Zargan, J., Chawla, R., Umar, S., & Khan, H. A. (2011). Upregulation of CSPG3 accompanies neuronal progenitor proliferation and migration in EAE. *Journal of Molecular Neuroscience*, 43(3), 531–540. <https://doi.org/10.1007/s12031-010-9476-0>
- Satoh, J. I., Tabunoki, H., & Yamamura, T. (2009). Molecular network of the comprehensive multiple sclerosis brain-lesion proteome. *Multiple Sclerosis*, 15(5), 531–541. <https://doi.org/10.1177/1352458508101943>
- Schirmer, L., Velmshch, D., Holmqvist, S., Kaufmann, M., Werneburg, S., Jung, D., ... Rowitch, D. H. (2019). Neuronal vulnerability and multi-lineage diversity in multiple sclerosis. *Nature*, 573, 75–82. <https://doi.org/10.1038/s41586-019-1404-z>
- Schreibelt, G., van Horssen, J., van Rossum, S., Dijkstra, C. D., Drukarch, B., & de Vries, H. E. (2007). Therapeutic potential and biological role of endogenous antioxidant enzymes in multiple sclerosis pathology. *Brain Research Reviews*, 56(2), 322–330. <https://doi.org/10.1016/j.brainresrev.2007.07.005>
- Scott-Drew, S., & ffrench-Constant, C. (1997). Expression and function of thrombospondin-1 in myelinating glial cells of the central nervous system. *Journal of Neuroscience Research*, 50(2), 202–214. [https://doi.org/10.1002/\(SICI\)1097-4547\(19971015\)50:2<202::AID-JNR9>3.0.CO;2-J](https://doi.org/10.1002/(SICI)1097-4547(19971015)50:2<202::AID-JNR9>3.0.CO;2-J)
- Selvaraju, R., Bernasconi, L., Losberger, C., Graber, P., Kadi, L., Avellana-Adalid, V., ... Boschert, U. (2004). Osteopontin is upregulated during in vivo demyelination and remyelination and enhances myelin formation in vitro. *Molecular and Cellular Neurosciences*, 25(4), 707–721. <https://doi.org/10.1016/j.mcn.2003.12.014>
- Sherman, L. S., Struve, J. N., Rangwala, R., Wallingford, N. M., Tuohy, T. M., Kuntz, C. (2002). Hyaluronate-based extracellular matrix: Keeping glia in their place. *Glia*, 38(2), 93–102. <https://doi.org/10.1002/glia.10053>
- Shin, S. L., Cha, J. H., Chun, M. H., Chung, J. W., & Lee, M. Y. (1999). Expression of osteopontin mRNA in the adult rat brain. *Neuroscience Letters*, 273(2), 73–76. [https://doi.org/10.1016/s0304-3940\(99\)00516-9](https://doi.org/10.1016/s0304-3940(99)00516-9)
- Shipley, J. M., Wesselschmidt, R. L., Kobayashi, D. K., Ley, T. J., & Shapiro, S. D. (1996). Metalloelastase is required for macrophage-mediated proteolysis and matrix invasion in mice. *Proceedings of the National Academy of Sciences of the United States of America*, 93(9), 3942–3946. <https://doi.org/10.1073/pnas.93.9.3942>
- Shiryaev, S. A., Savinov, A. Y., Cieplak, P., Ratnikov, B. I., Motamedchaboki, K., Smith, J. W., & Strongin, A. Y. (2009). Matrix metalloproteinase proteolysis of the myelin basic protein isoforms is a source of immunogenic peptides in autoimmune multiple sclerosis. *PLoS ONE*, 4(3), e4952. <https://doi.org/10.1371/journal.pone.0004952>
- Siebert, J. R., & Osterhout, D. J. (2011). The inhibitory effects of chondroitin sulfate proteoglycans on oligodendrocytes. *Journal of Neurochemistry*, 119(1), 176–188. <https://doi.org/10.1111/j.1471-4159.2011.07370.x>
- Siebert, J. R., Stelzner, D. J., & Osterhout, D. J. (2011). Chondroitinase treatment following spinal contusion injury increases migration of oligodendrocyte progenitor cells. *Experimental Neurology*, 231(1), 19–29. <https://doi.org/10.1016/j.expneurol.2011.05.002>
- Sikkema, A. H., Stoffels, J. M. J., Wang, P., Basedow, F. J., Buisink, R., Bajramovic, J. J., & Baron, W. (2018). Fibronectin aggregates promote features of a classically and alternatively activated phenotype in macrophages. *Journal of Neuroinflammation*, 15(1), 218. <https://doi.org/10.1186/s12974-018-1238-x>
- Sim, F. J., Zhao, C., Penderis, J., & Franklin, R. J. (2002). The age-related decrease in CNS remyelination efficiency is attributable to an impairment of both oligodendrocyte progenitor recruitment and differentiation. *Journal of Neuroscience*, 22(7), 2451–2459. <https://doi.org/10.1523/JNEUROSCI.22-07-02451.2002>
- Sinclair, C., Mirakhor, M., Kirk, J., Farrell, M., & McQuaid, S. (2005). Up-regulation of osteopontin and alphaBeta-crystallin in the normal-appearing white matter of multiple sclerosis: An immunohistochemical study utilizing tissue microarrays. *Neuropathology and Applied Neurobiology*, 31(3), 292–303. <https://doi.org/10.1111/j.1365-2990.2004.00638.x>

- Singh, P., Carraher, C., & Schwarzbauer, J. E. (2010). Assembly of fibronectin extracellular matrix. *Annual Review of Cell and Developmental Biology*, 26, 397–419. <https://doi.org/10.1146/annurev-cellbio-100109-104020>
- Siri, A., Knauper, V., Veirana, N., Caocci, F., Murphy, G., & Zardi, L. (1995). Different susceptibility of small and large human tenascin-C isoforms to degradation by matrix metalloproteinases. *Journal of Biological Chemistry*, 270(15), 8650–8654. <https://doi.org/10.1074/jbc.270.15.8650>
- Siskova, Z., Baron, W., de Vries, H., & Hoekstra, D. (2006). Fibronectin impedes “myelin” sheet-directed flow in oligodendrocytes: A role for a beta 1 integrin-mediated PKC signaling pathway in vesicular trafficking. *Molecular and Cellular Neurosciences*, 33(2), 150–159. <https://doi.org/10.1016/j.mcn.2006.07.001>
- Siskova, Z., Yong, V. W., Nomden, A., van Strien, M., Hoekstra, D., & Baron, W. (2009). Fibronectin attenuates process outgrowth in oligodendrocytes by mislocalizing MMP-9 activity. *Molecular and Cellular Neurosciences*, 42(3), 234–242. <https://doi.org/10.1016/j.mcn.2009.07.005>
- Sixt, M., Engelhardt, B., Pausch, F., Hallmann, R., Wendler, O., & Sorokin, L. M. (2001). Endothelial cell laminin isoforms, laminins 8 and 10, play decisive roles in T cell recruitment across the blood-brain barrier in experimental autoimmune encephalomyelitis. *Journal of Cell Biology*, 153(5), 933–946. <https://doi.org/10.1083/jcb.153.5.933>
- Skipuletz, T., Gudi, V., Hackstette, D., & Stangel, M. (2011). De- and remyelination in the CNS white and grey matter induced by cuprizone: The old, the new, and the unexpected. *Histology and Histopathology*, 26(12), 1585–1597. <https://doi.org/10.14670/HH-26.1585>
- Škuljec, J., Gudi, V., Ulrich, R., Frichert, K., Yildiz, Ö., Pul, R., ... Stangel, M. (2011). Matrix metalloproteinases and their tissue inhibitors in cuprizone-induced demyelination and remyelination of brain white and gray matter. *Journal of Neuropathology and Experimental Neurology*, 70(9), 758–769. <https://doi.org/10.1097/NEN.0b013e3182294fad>
- Sloane, J. A., Batt, C., Ma, Y., Harris, Z. M., Trapp, B., & Vartanian, T. (2010). Hyaluronan blocks oligodendrocyte progenitor maturation and remyelination through TLR2. *Proceedings of the National Academy of Sciences of the United States of America*, 107(25), 11555–11560. <https://doi.org/10.1073/pnas.1006496107>
- Smith, K. J., Blakemore, W. F., & McDonald, W. I. (1979). Central remyelination restores secure conduction. *Nature*, 280(5721), 395–396. <https://doi.org/10.1038/280395a0>
- Smith, M. E., & Eng, L. F. (1987). Glial fibrillary acidic protein in chronic relapsing experimental allergic encephalomyelitis in SJL/J mice. *Journal of Neuroscience Research*, 18(1), 203–208. <https://doi.org/10.1002/jnr.490180129>
- Sobel, R. A., & Ahmed, A. S. (2001). White matter extracellular matrix chondroitin sulfate/dermatan sulfate proteoglycans in multiple sclerosis. *Journal of Neuropathology and Experimental Neurology*, 60(12), 1198–1207. <https://doi.org/10.1093/jnen/60.12.1198>
- Sobel, R. A., Chen, M., Maeda, A., & Hinojoza, J. R. (1995). Vitronectin and integrin vitronectin receptor localization in multiple sclerosis lesions. *Journal of Neuropathology and Experimental Neurology*, 54(2), 202–213. <https://doi.org/10.1097/00005072-199503000-00007>
- Sobel, R. A., Hinojoza, J. R., Maeda, A., & Chen, M. (1998). Endothelial cell integrin laminin receptor expression in multiple sclerosis lesions. *American Journal of Pathology*, 153(2), 405–415. [https://doi.org/10.1016/S0002-9440\(10\)65584-8](https://doi.org/10.1016/S0002-9440(10)65584-8)
- Sobel, R. A., & Mitchell, M. E. (1989). Fibronectin in multiple sclerosis lesions. *American Journal of Pathology*, 135(1), 161–168.
- Sofroniew, M. V., & Vinters, H. V. (2010). Astrocytes: Biology and pathology. *Acta Neuropathologica*, 119(1), 7–35. <https://doi.org/10.1007/s00401-009-0619-8>
- Stephenson, E. L., Mishra, M. K., Moussienko, D., Laflamme, N., Rivest, S., Ling, C. C., & Yong, V. W. (2018). Chondroitin sulfate proteoglycans as novel drivers of leucocyte infiltration in multiple sclerosis. *Brain*, 141(4), 1094–1110. <https://doi.org/10.1093/brain/awy033>
- Stoffels, J. M. J., de Jonge, J. C., Stancic, M., Nomden, A., van Strien, M. E., Ma, D., ... Baron, W. (2013). Fibronectin aggregation in multiple sclerosis lesions impairs remyelination. *Brain*, 136(Pt 1), 116–131. <https://doi.org/10.1093/brain/aww313>
- Stoffels, J. M., Hoekstra, D., Franklin, R. J., Baron, W., & Zhao, C. (2015). The EIIIA domain from astrocyte-derived fibronectin mediates proliferation of oligodendrocyte progenitor cells following CNS demyelination. *Glia*, 63(2), 242–256. <https://doi.org/10.1002/glia.22748>
- Stracke, J. O., Hutton, M., Stewart, M., Pendás, A. M., Smith, B., López-Otin, C., ... Knäuper, V. (2000). Biochemical characterization of the catalytic domain of human matrix metalloproteinase 19. Evidence for a role as a potent basement membrane degrading enzyme. *Journal of Biological Chemistry*, 275(20), 14809–14816. <https://doi.org/10.1074/jbc.275.20.14809>
- Strijbis, E. M. M., Kooi, E. J., van der Valk, P., & Geurts, J. J. G. (2017). Cortical remyelination is heterogeneous in multiple sclerosis. *Journal of Neuropathology and Experimental Neurology*, 76(5), 390–401. <https://doi.org/10.1093/jnen/nlx023>
- Stys, P. K., Zamponi, G. W., van Minnen, J., & Geurts, J. J. (2012). Will the real multiple sclerosis please stand up? *Nature Reviews Neuroscience*, 13(7), 507–514. <https://doi.org/10.1038/nrn3275>
- Sun, Y., Deng, Y., Xiao, M., Hu, L., Li, Z., & Chen, C. (2017). Chondroitin sulfate proteoglycans inhibit the migration and differentiation of oligodendrocyte precursor cells and its counteractive interaction with laminin. *International Journal of Molecular Medicine*, 40(6), 1657–1668. <https://doi.org/10.3892/ijmm.2017.3153>
- Taraboletti, G., Morbidelli, L., Donnini, S., Parenti, A., Granger, H. J., Giavazzi, R., Ziche, M. (2000). The heparin binding 25 kDa fragment of thrombospondin-1 promotes angiogenesis and modulates gelatinase and TIMP-2 production in endothelial cells. *The FASEB Journal*, 14(12), 1674–1676. <https://doi.org/10.1096/fj.99-0931fje>
- Theocharis, A. D., Skandalis, S. S., Gialeli, C., & Karamanos, N. K. (2016). Extracellular matrix structure. *Advanced Drug Delivery Reviews*, 97, 4–27. <https://doi.org/10.1016/j.addr.2015.11.001>
- Torkildsen, O., Brunborg, L. A., Myhr, K. M., & Bo, L. (2008). The cuprizone model for demyelination. *Acta Neurologica Scandinavica*, 117(Suppl. 188), 72–76. <https://doi.org/10.1111/j.1600-0404.2008.01036.x>
- Trapp, B. D., & Nave, K. A. (2008). Multiple sclerosis: An immune or neurodegenerative disorder? *Annual Review of Neuroscience*, 31, 247–269. <https://doi.org/10.1146/annurev.neuro.30.051606.094313>
- Tripathi, A., Parikh, Z. S., Vora, P., Frost, E. E., & Pillai, P. P. (2017). pERK1/2 peripheral recruitment and filopodia protrusion augment oligodendrocyte progenitor cell migration: Combined effects of PDGF-A and fibronectin. *Cellular and Molecular Neurobiology*, 37(2), 183–194. <https://doi.org/10.1007/s10571-016-0359-y>
- Uhm, J. H., Dooley, N. P., Oh, L. Y., & Yong, V. W. (1998). Oligodendrocytes utilize a matrix metalloproteinase, MMP-9, to extend processes along an astrocyte extracellular matrix. *Glia*, 22(1), 53–63. [https://doi.org/10.1002/\(SICI\)1098-1136\(199801\)22:1<53::AID-GLIA5>3.0.CO;2-9](https://doi.org/10.1002/(SICI)1098-1136(199801)22:1<53::AID-GLIA5>3.0.CO;2-9)
- Ulrich, R., Baumgartner, W., Gerhauser, I., Seeliger, F., Haist, V., Deschl, U., & Alldinger, S. (2006). MMP-12, MMP-3, and TIMP-1 are markedly upregulated in chronic demyelinating theiler murine encephalomyelitis. *Journal of Neuropathology and Experimental Neurology*, 65(8), 783–793. <https://doi.org/10.1097/01.jnen.0000229990.32795.0d>
- Ulrich, R., Seeliger, F., Kreutzer, M., Germann, P. G., & Baumgartner, W. (2008). Limited remyelination in Theiler's murine encephalomyelitis due to insufficient oligodendroglial differentiation of nerve/glial antigen 2 (NG2)-positive putative oligodendroglial progenitor cells. *Neuropathology and Applied Neurobiology*, 34(6), 603–620. <https://doi.org/10.1111/j.1365-2990.2008.00956.x>
- van der Valk, P., & De Groot, C. J. (2000). Staging of multiple sclerosis (MS) lesions: Pathology of the time frame of MS. *Neuropathology and Applied Neurobiology*, 26(1), 2–10. <https://doi.org/10.1046/j.1365-2990.2000.00217.x>

- van Horssen, J., Bo, L., Vos, C. M., Virtanen, I., & de Vries, H. E. (2005). Basement membrane proteins in multiple sclerosis-associated inflammatory cuffs: Potential role in influx and transport of leukocytes. *Journal of Neuropathology and Experimental Neurology*, 64(8), 722–729. <https://doi.org/10.1097/01.jnen.0000173894.09553.13>
- van Horssen, J., Dijkstra, C. D., & de Vries, H. E. (2007). The extracellular matrix in multiple sclerosis pathology. *Journal of Neurochemistry*, 103(4), 1293–1301. <https://doi.org/10.1111/j.1471-4159.2007.04897.x>
- van Horssen, J., Vos, C. M., Admiraal, L., van Haastert, E. S., Montagne, L., van der Valk, P., & de Vries, H. E. (2006). Matrix metalloproteinase-19 is highly expressed in active multiple sclerosis lesions. *Neuropathology and Applied Neurobiology*, 32(6), 585–593. <https://doi.org/10.1111/j.1365-2990.2006.00766.x>
- Van Hove, I., Lemmens, K., Van de Velde, S., Verslegers, M., & Moons, L. (2012). Matrix metalloproteinase-3 in the central nervous system: A look on the bright side. *Journal of Neurochemistry*, 123(2), 203–216. <https://doi.org/10.1111/j.1471-4159.2012.07900.x>
- Vogel, D. Y. S., Vereyken, E. J. F., Glim, J. E., Heijnen, P. D. A. M., Moeton, M., van der Valk, P., ... Dijkstra, C. D. (2013). Macrophages in inflammatory multiple sclerosis lesions have an intermediate activation status. *Journal of Neuroinflammation*, 10, 35. <https://doi.org/10.1186/1742-2094-10-35>
- Vos, C. M., van Haastert, E. S., de Groot, C. J., van der Valk, P., & de Vries, H. E. (2003). Matrix metalloproteinase-12 is expressed in phagocytotic macrophages in active multiple sclerosis lesions. *Journal of Neuroimmunology*, 138(1–2), 106–114. [https://doi.org/10.1016/S0165-5728\(03\)00036-5](https://doi.org/10.1016/S0165-5728(03)00036-5)
- Wang, P., Gorter, R. P., de Jonge, J. C., Nazmuddin, M., Zhao, C., Amor, S., ... Baron, W. (2018). MMP7 cleaves remyelination-impairing fibronectin aggregates and its expression is reduced in chronic multiple sclerosis lesions. *Glia*, 66(8), 1625–1643. <https://doi.org/10.1002/glia.23328>
- Wang, W., Wang, J., & Li, F. (2017). Hyaluronidase and Chondroitinase. *Advances in Experimental Medicine and Biology*, 925, 75–87. https://doi.org/10.1007/5584_2016_54
- Watanabe, M., Hadzic, T., & Nishiyama, A. (2004). Transient upregulation of Nkx2.2 expression in oligodendrocyte lineage cells during remyelination. *Glia*, 46(3), 311–322. <https://doi.org/10.1002/glia.20006>
- Waubant, E., Goodkin, D. E., Gee, L., Bacchetti, P., Sloan, R., Stewart, T., ... Miller, K. (1999). Serum MMP-9 and TIMP-1 levels are related to MRI activity in relapsing multiple sclerosis. *Neurology*, 53(7), 1397–1401. <https://doi.org/10.1212/wnl.53.7.1397>
- Weaver, A., Goncalves da Silva, A., Nuttall, R. K., Edwards, D. R., Shapiro, S. D., Rivest, S., & Yong, V. W. (2005). An elevated matrix metalloproteinase (MMP) in an animal model of multiple sclerosis is protective by affecting Th1/Th2 polarization. *The FASEB Journal*, 19(12), 1668–1670. <https://doi.org/10.1096/fj.04-2030fje>
- Werner, S. R., Dotzla, J. E., & Smith, R. C. (2008). MMP-28 as a regulator of myelination. *BMC Neuroscience*, 9, 83. <https://doi.org/10.1186/1471-2202-9-83>
- Williams, A., Piaton, G., & Lubetzki, C. (2007). Astrocytes—friends or foes in multiple sclerosis? *Glia*, 55(13), 1300–1312. <https://doi.org/10.1002/glia.20546>
- Wolswijk, G. (1998). Chronic stage multiple sclerosis lesions contain a relatively quiescent population of oligodendrocyte precursor cells. *Journal of Neuroscience*, 18(2), 601–609. <https://doi.org/10.1523/JNEUROSCI.18-02-00601.1998>
- Woodroffe, M. N., Bellamy, A. S., Feldmann, M., Davison, A. N., & Cuzner, M. L. (1986). Immunocytochemical characterisation of the immune reaction in the central nervous system in multiple sclerosis. Possible role for microglia in lesion growth. *Journal of the Neurological Sciences*, 74(2–3), 135–152. [https://doi.org/10.1016/0022-510X\(86\)90100-0](https://doi.org/10.1016/0022-510X(86)90100-0)
- Yao, L., Phan, F., & Li, Y. (2013). Collagen microsphere serving as a cell carrier supports oligodendrocyte progenitor cell growth and differentiation for neurite myelination in vitro. *Stem Cell Research & Therapy*, 4(5), 109. <https://doi.org/10.1186/scrt320>
- Yeung, M. S. Y., Djelloul, M., Steiner, E., Bernard, S., Salehpour, M., Possnert, G., ... Frisén, J. (2019). Dynamics of oligodendrocyte generation in multiple sclerosis. *Nature*, 566(7745), 538–542. <https://doi.org/10.1038/s41586-018-0842-3>
- Yong, V. W. (2005). Metalloproteinases: Mediators of pathology and regeneration in the CNS. *Nature Reviews Neuroscience*, 6(12), 931–944. <https://doi.org/10.1038/nrn1807>
- Yong, V. W., Power, C., Forsyth, P., & Edwards, D. R. (2001). Metalloproteinases in biology and pathology of the nervous system. *Nature Reviews Neuroscience*, 2(7), 502–511. <https://doi.org/10.1038/35081571>
- Zawadzka, M., Rivers, L. E., Fancy, S. P. J., Zhao, C., Tripathi, R., Jamen, F., ... Franklin, R. J. M. (2010). CNS-resident glial progenitor/stem cells produce Schwann cells as well as oligodendrocytes during repair of CNS demyelination. *Cell Stem Cell*, 6(6), 578–590. <https://doi.org/10.1016/j.stem.2010.04.002>
- Zeger, M., Popken, G., Zhang, J., Xuan, S., Lu, Q. R., Schwab, M. H., ... Ye, P. (2007). Insulin-like growth factor type 1 receptor signaling in the cells of oligodendrocyte lineage is required for normal in vivo oligodendrocyte development and myelination. *Glia*, 55(4), 400–411. <https://doi.org/10.1002/glia.20469>
- Zeis, T., Howell, O. W., Reynolds, R., & Schaeren-Wiemers, N. (2018). Molecular pathology of multiple sclerosis lesions reveals a heterogeneous expression pattern of genes involved in oligodendroglioneogenesis. *Experimental Neurology*, 305, 76–88. <https://doi.org/10.1016/j.expneurol.2018.03.012>
- Zendedel, A., Kashani, I. R., Azimzadeh, M., Pasbakhsh, P., Omid, N., Golestani, A., ... Clarner, T. (2016). Regulatory effect of triiodothyronine on brain myelination and astrogliosis after cuprizone-induced demyelination in mice. *Metabolic Brain Disease*, 31(2), 425–433. <https://doi.org/10.1007/s11011-015-9781-y>
- Zhao, C., Fancy, S. P. J., French-Constant, C., & Franklin, R. J. M. (2008). Osteopontin is extensively expressed by macrophages following CNS demyelination but has a redundant role in remyelination. *Neurobiology of Diseases*, 31(2), 209–217. <https://doi.org/10.1016/j.nbd.2008.04.007>
- Zhao, C., Fancy, S. P., Franklin, R. J., & French-Constant, C. (2009). Up-regulation of oligodendrocyte precursor cell alphaV integrin and its extracellular ligands during central nervous system remyelination. *Journal of Neuroscience Research*, 87(15), 3447–3455. <https://doi.org/10.1002/jnr.22231>
- Zhao, C., Li, W. W., & Franklin, R. J. (2006). Differences in the early inflammatory responses to toxin-induced demyelination are associated with the age-related decline in CNS remyelination. *Neurobiology of Aging*, 27(9), 1298–1307. <https://doi.org/10.1016/j.neurobiolaging.2005.06.008>
- Zuo, J., Ferguson, T. A., Hernandez, Y. J., Stetler-Stevenson, W. G., & Muir, D. (1998). Neuronal matrix metalloproteinase-2 degrades and inactivates a neurite-inhibiting chondroitin sulfate proteoglycan. *Journal of Neuroscience*, 18(14), 5203–5211. <https://doi.org/10.1523/JNEUROSCI.18-14-05203.1998>

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

Transparent Peer Review Report

How to cite this article: de Jong JM, Wang P, Oomkens M, Baron W. Remodeling of the interstitial extracellular matrix in white matter multiple sclerosis lesions: Implications for remyelination (failure). *J Neuro Res*. 2020;00:1–28. <https://doi.org/10.1002/jnr.24582>